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Division of Computer Research and Technology
Fiscal Year 1984 Annual Report
Volume II

DCRT
20TH
ANNIVERSARY

U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

Division of Computer Research and Technology

Fiscal Year 1984 Annual Report
Volume II

U.S. DEPARTMENT OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes of Health

Foreword

The Division of Computer Research and Technology has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. DCRT serves as a scientific and technological resource for other parts of PHS, and for other Federal organizations with biomedical and statistical computing needs.

DCRT programs focus on three primary activities: conducting research, developing computer systems, and providing computer facilities.

The *DCRT Fiscal Year 1984 Annual Report* describes our work in two volumes:

Volume 1 gives an overview of the work of each group, highlighting the year's accomplishments;
Volume 2 gives details about the projects and activities of each group.

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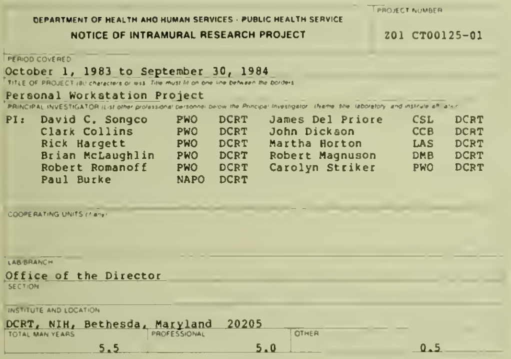
Personal Workstation Project--Word Processing Subproject **84**

The Personal Workstation Office began operation this fiscal year by developing and providing a series of personal computer courses. Robert A. Magnuson, Deputy Assistant for Software Development in DCRT's Data Management Branch, was one of the instructors.

Office of the Director

Arnold W. Pratt, M.D., Director

Research Projects



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00125-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Personal Workstation Project

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	David C. Songco	PWO	DCRT	James Del Priore	CSL	DCRT
	Clark Collins	PWO	DCRT	John Dickson	CCB	DCRT
	Rick Hargett	PWO	DCRT	Martha Horton	LAS	DCRT
	Brian McLaughlin	PWO	DCRT	Robert Magnuson	DMB	DCRT
	Robert Romanoff	PWO	DCRT	Carolyn Striker	PWO	DCRT
	Paul Burke	NAPO	DCRT			

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Director

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
5.5	5.0	0.5

Personal Workstation Project

This project was initiated in FY83 to determine how effectively personal computer workstations could be used at NIH. The investigation included PC access to the central facility with reliable file transfer as well as local computing functions such as text editing, manipulation of numeric data, generation of graphic displays, and collecting and storing data for selective retrieval.

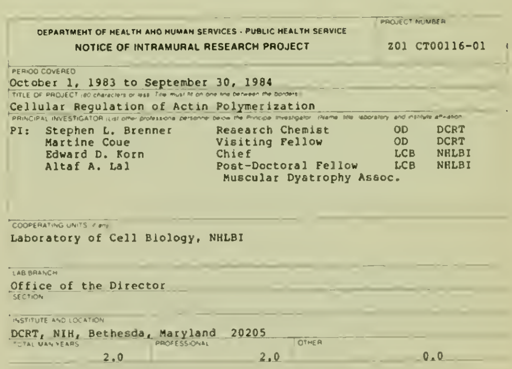
During the first part of FY84 representatives from throughout DCRT were organized into over a dozen groups to select, test, and evaluate hardware and software products of potential use to the NIH community. Workstations based on the IBM Personal Computer were purchased and used to determine a set of commercially available products that could be integrated and supported by DCRT.

The evaluation committees submitted reports on their functional areas by June 1984. These reports were used to develop a plan for providing coordinated support to personal computer users at NIH. At the same time a group of full-time PC specialists were brought together to form the Personal Workstation Office (PWO).

The PWO began operation by developing and providing a series of courses on personal computer topics during DCRT's summer training session with a full schedule planned for the Fall. The PWO also began answering telephone inquires and other requests for help from the NIH user community.

The user support system is based on the establishment of a network of key PC users in the various BID's combined with a referral system of experts from within DCRT. With this two-pronged approach the central PWO is able to provide comprehensive support with a minimum of staff. In addition, the BID's will be better equipped to deal with their own local processing applications and problems.

Continued refinement and integration of PC products and user support is planned for FY85, in keeping with our plan to provide coordinated support for personal computer users at NIH. Specific areas include the development of a comprehensive PC users guide, the publication of a PC newsletter, and the establishment of a walk-in demonstration center.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00116-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Cellular Regulation of Actin Polymerization

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Stephen L. Brenner	Research Chemist	OD	DCRT
	Martine Coue	Visiting Fellow	OD	DCRT
	Edward D. Korn	Chief	LCB	NHLBI
	Altaf A. Lal	Post-Doctoral Fellow Muscular Dystrophy Assoc.	LCB	NHLBI

COOPERATING UNITS (if any)
Laboratory of Cell Biology, NHLBI

LAB/BRANCH
Office of the Director

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
2.0	2.0	0.0

Cellular Regulation of Actin Polymerization

The assembly and disassembly of F-actin polymers from G-actin monomers is both spatially and temporally regulated in eukaryotic cells. This regulation is vital to cell motility, endocytosis, and cell division. We have continued our in vitro studies on actin polymerization and its regulation by purified proteins. Rate constants have been determined for the polymerization process by quantitative analysis of assembly progress curves and the use of chemically cross-linked actin trimers as seeds for assembly. Comparison of ADP-actin and ATP-actin has shown that nucleotide hydrolysis is not required for assembly, but that the rate constants for assembly are higher, and for disassembly are smaller, when ATP is present.

Brevin, a protein that interacts with the ends of actin polymers, has been purified to homogeneity from bovine plasma. In the presence of micromolar calcium, brevin nucleates actin filament assembly while severing preformed actin polymers. In both cases the brevin remains bound to one end of the resultant polymers. Brevin forms stable complexes with as few as two actin monomers. Using fluorescent assays with pyrenyl- and NBD-labelled actin, and using actin with bound ADP and ATP, we have begun to dissect the mechanism of action of brevin.

Publications:

Brenner, S.L., and Korn, E.D.: Evidence that F-actin can hydrolyze ATP independent of monomer-polymer end interactions. *J. Biol. Chem.* 259: 1441, 1984.

Brenner, S.L., and Korn, E.D.: On the mechanism of actin monomer-polymer subunit exchange at steady state. *J. Biol. Chem.* 258: 5013, 1983.

Brenner, S.L., Tobacman, L.S., and Korn, E.D.: The kinetics of actin polymerization and monomer-polymer subunit exchange at steady state. In Dos Remedios, C. (Ed.): *Actin: Structure and Function in Muscle and Non-Muscle cells.* New York, Academic Press, 1983, pp. 97-106.

Lal, A.A., Korn, E.D., and Brenner, S.L.: Rate constants for actin polymerization in ATP determined using cross-linked actin trimers as nuclei. *J. Biol. Chem.* (in press).

Pantaloni, D., Carlier, M.-F., Coue, M., Lal, A.A., Brenner, S.L., and Korn, E.D.: The critical concentration of actin in the presence of ATP increases with the number concentration of filaments and approaches the critical concentration of actin ADP. *J. Biol. Chem.* 259, 1984.

Tobacman, L.S., Brenner, S.L., and Korn, E.D.: Effects of Acanthamoeba profilin on the pre-steady state kinetics of actin polymerization and on the concentration of F-actin at steady-state. *J. Biol. Chem.* 258: 8804, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00113-02

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Computer System for Macromolecular and Cellular Graphics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Richard Feldmann	OD	DCRT
	Michael Potter	LG/DCBD	NCI
	Eric Henry	LCP	NIADDK
	Jane Small	CCB	DCRT
	Horace Cascio	BEIB	DRS

COOPERATING UNITS *(if any)*

LAB/BRANCH
Office of the Director

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	1.0	1.0

A Computer System for Macromolecular and Cellular Graphics

Specifications for a computer graphics system employing the most advanced commercially available hardware were developed in the preceeding fiscal year. Conversion of software from various earlier computer systems to the new hardware began in the summer of 1983 and was completed in the spring of 1984. Software for new hardware units is being developed.

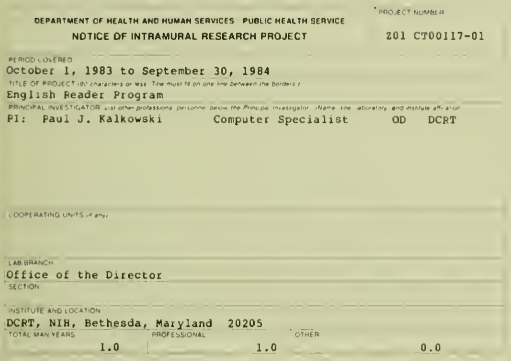
The system when operational will permit the modeling of macromolecular structures from protein sequences using energy minimization calculations. The array processor, which is part of the system, will supply these energy calculations at the rate of 100 million floating point operations per second. The graphics components of the system will permit the user to see the molecular structure in stereo and color in either line or surface representation mode.

Two three-dimensional manipulation units designed and implemented by Horace Cascio will permit the user to tell the computational and graphics components more easily how to change the molecular structure.

The other graphics components will permit the generation and display of general surfaces such as those found in cellular and subcellular structures.

Software was purchased and is being developed to permit modeling of these types of surfaces.

The images developed on the system can be transmitted to scientific audiences by slide film, movie film, videotape, and eventually, by videodisk.



PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CT00117-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
English Reader Program

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: Paul J. Kalkowski Computer Specialist OD DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Office of the Director

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

English Reader Program

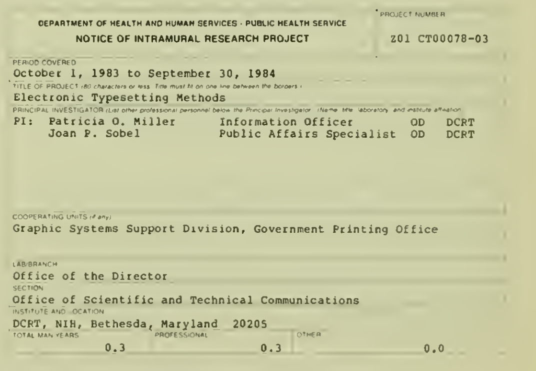
The English Reader Program is a computer program that reads English language text, parses sentences, and creates an index. Its execution is controlled by a set of user-written statements that specify program options and define the format of the input data set.

The input data set may consist of records containing fields of English text, or it may consist of lines of text for an article, book, etc.

The program extracts words from its input data, then looks them up in an online dictionary of English and finds their possible parts of speech. Information about words can also be obtained by analysis of inflectional endings, prefixes, and suffixes. Standard rules of spelling can be applied to find base words in the dictionary from which text words are derived. Then, the program applies rules of syntax to the words in a sentence, taking into account the context of each word and its parts of speech; and possible functions and relations of words are determined. Finally, sentences are scanned for terms and phrases to be indexed.

The dictionary of English contains at present more than 72,000 vocabulary entries and their parts of speech. In addition to the English dictionary, the program may employ an auxiliary dictionary containing technical terms used in a particular field of knowledge. Synonyms and hierarchical terms can be defined in the auxiliary dictionary, so that when the program finds terms in English text, it can index them with references to their related terms.

The program produces two permanent WYLBUR data sets with each execution: a data set of terms, which can be used to construct an auxiliary dictionary; and a data set of index entries, which can be used to produce a printed index, or which may serve as input for the user's information retrieval system.



PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CT00078-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Electronic Typesetting Methods

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: Patricia O. Miller Information Officer OD DCRT
Joan P. Sobel Public Affairs Specialist OD DCRT

COOPERATING UNITS (if any)
Graphic Systems Support Division, Government Printing Office

LAB/BRANCH
Office of the Director

SECTION
Office of Scientific and Technical Communications

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

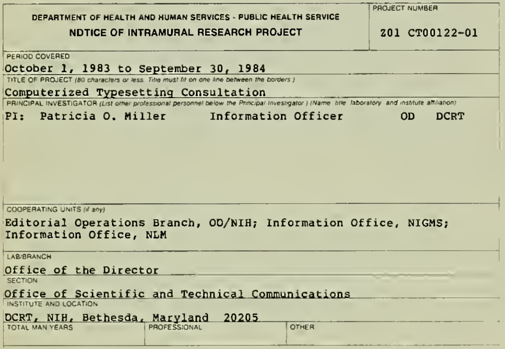
TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Electronic Typesetting Methods

This project, begun in FY81, involves collecting and encoding text on magnetic tape for typesetting by GPO. Eliminating rekeying by a typesetter, and thus the galley proof stage of production, has cut typsetting costs 80 percent. Methods standardized in FY82 have been analyzed continually.

This year, codes were developed for inserting graphics of variable sizes appropriately within text.

Future plans include exploration of the generic coding concept, as well as suitable state-of-the-art systems in use by the private sector.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00122-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Computerized Typesetting Consultation

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: Patricia O. Miller Information Officer OD DCRT

COOPERATING UNITS (if any)
Editorial Operations Branch, OD/NIH; Information Office, NIGMS; Information Office, NLM

LAB/BRANCH
Office of the Director

SECTION
Office of Scientific and Technical Communications

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER

Computerized Typesetting Consultation

DCRT techniques for using WYLBUR to prepare text for direct input to computerized typesetting systems have been made available to others in the NIH public affairs community.

Consultations with BID's include: NIGMS (methods for preparing the annual cell repository directory); NLM (feasibility for preparing technical reports); and the Editorial Operations Branch, OD/NIH (GPO design sessions, planning advice for the NIH Scientific Directory/Bibliography).

Employees of the NIH Central Computer Utility keep the system reliable 24 hours a day, seven days a week. Supervisory Computer Operator Ramon J. Alvarado has been with DCRT for 20 years.

Computer Center Branch

Joseph D. Naughton, Chief

Microprocessor Support

Transferring data between microcomputers and the NIH Computer Utility was made reliable this year with the installation of two communications packages: KERMIT on the DECsystem-10 and UCLA/FTP on the IBM 3081. Utilizing a packet-based communications protocol, these packages ensure error-free transmission of data and programs between the microcomputer and the Computer Utility.

KERMIT and UCLA/FTP software on the NIH mainframe computers vastly increase the power and versatility of microcomputers at NIH. Microcomputers not only can function as terminals, they also can access the processing power of the Computer Utility for tasks that exceed the capability of the microcomputer. The Utility's wide variety of software, processing speed, data storage capacity, and centralized institutional data files are instantly available to microcomputer users, as are special-purpose peripherals (plotters, printers, and microfiche output devices).

Because the use of these protocols require companion programs running at each end of the communications link, software for IBM, Apple, and Osborne microcomputers was provided to registered users on diskettes. In addition, communications parameters for the IBM 3081 and the DECsystem-10 timesharing services were published, making it possible for microcomputer users to tailor their communications software to permit a microcomputer to be used as a terminal with the NIH mainframe computers.

System Security

Security has always been a primary consideration of the Computer Center. Required by law to provide security facilities to control access to the NIH Computer Utility and ensure the confidentiality of data stored on it, the Computer Center implemented phase I of the installation of the Resource Access Control Facility (RACF) last year. In FY84, data sets protected by RACF were made accessible through WYLBUR and TSO as well as batch on the IBM 3081 facility. Users now can control access to data sets stored on any direct access storage device using all standard batch and interactive services provided by the NIH Computer Utility. RACF enables owners of protected data sets to allow other individuals or groups one of four levels of access: NONE, READ, UPDATE, or ALTER. Thus, owners can completely control which users are allowed to access a data set and what access those users have to the data set.

Communications Link

Communications between the DECsystem-10 and the IBM 3081 was strengthened by the installation of new communications hardware and software on the DECsystem-10. Two new microprocessor-based controllers, called "Protocol Converters," were installed on two different DECsystem-10 front-end communications computers to enhance data transfer between the two mainframes. The new configuration allows data transfer to take place in both directions at once. Several obsolete hardware components were removed. Newly designed software improved system reliability and simplified problem resolution by reducing the number of programs involved and by providing flexible debugging tools. The transition took place without requiring any changes to user programs or procedures.

New Hardware

New interactive display terminals, designated the NIH8188, replaced all NIH7000 terminals this year. Manufactured by Megadata Corporation, the NIH8188 is user-friendly, featuring screen width selection of 80 or 132 characters, horizontal and vertical scrolling, 32K internal memory, automatic logon, and 32 function keys that can be programmed by the user and are maintained across power off periods.

Letter-quality hardcopy terminals were offered to users of WYLBUR, TSO, and the DECsystem-10 as a replacement for the CT45 terminal. The PSC-3101, manufactured by Printer Systems Corporation, uses daisy wheel technology to produce high-quality type much faster than the CT45, printing bidirectionally at 55 cps. The terminal has 10 programmable function keys that remain programmed after the power is turned off.

A remote laser printer, the IBM 6670 Information Distributor, was made available to users this year. The 6670 uses an electrographic process to produce high-quality output on letter-size or legal-size cut sheets of paper. Though slower than other remote printers, the 6670 offers a number of unique capabilities: two-sided printing, multiple copies, a variety of type styles (including 10-pitch, 12-pitch, and proportionally-spaced styles), and the ability to print Greek letters, mathematical symbols, and subscripts or superscripts.

Software Additions

Data set integrity was strengthened this year with the installation of cross-system enqueue. This data set protection feature is particularly important in the multiple CPU, shared Direct Access Storage Device (DASD) environment of the NIH Computer Utility, especially with the dual WYLBURs installed this year. Cross-system enqueue prevents the accidental destruction of data by users attempting to simultaneously modify the same data set from different CPU's. Data set access is recognized and controlled across all CPU's in the system, applying automatically to data sets accessed through WYLBUR, TSO, and batch.

The IBM Interactive System Productivity Facility (ISPF) and the Program Development Facility (PDF) were made available for interactive use under TSO by 3270-type terminals. Aimed primarily at professional programmers, ISPF provides the controls and services necessary to support the processing of user-written interactive application dialogs.

A TSO Command List Compiler, SLR8, was installed on the IBM 3081 facility to enable TSO users to compile their command lists once, and use them repetitively. SLR8 saves time and offers users increased flexibility and improved performance.

Producing foils (transparencies for overhead projection) became easier this year with the introduction of FOIL3800. Used with WYLBUR, FOIL3800 can produce high-quality, large character, printed output in standard or italic type on the IBM 3800 laser printer. The output can then be used with any copying machine capable of producing transparencies to create professional-looking foils.

A number of long-established software packages for both the IBM 3081 and the DECsystem-10 were updated with new releases this year. DECsystem-10 users saw an improved version of BRIGHT--the scientific data manipulation system for entering, storing, and analyzing data--that was enhanced to incorporate many features and refinements suggested by BRIGHT users. A new release of POSTER added six new commands and a standard output file. New versions of TELL-A-GRAF and DISSPLA significantly enhanced the graphics capability of the IBM 3081 facility and allowed the final retirement of the old Integrated Plotting Package.

Training, Assistance, and Documentation

The Independent Training Assisted by Computer (ABC) system introduced last year was received enthusiastically by the NIH user community. The 40-lesson printed text, *Introduction to WYLBUR,* was sent to 495 users, and more then 2,500 users utilized the course during FY84. Credit was granted to 719 students who successfully completed the entire course.

The multimedia self-study program was expanded this year to include four new offerings. A course on *VS FORTRAN* and three courses in the *Creating an OS/VS Program* series were added.

Despite such efforts to provide alternative training opportunities, the Training Unit again received more requests for classroom courses than it could fill. 5,535 applications for formal training were submitted and 3,063 students were accommodated in 140 sessions of 53 different courses. Six new courses were offered during the 1984 training year, which was shifted this year to begin in October rather than in the spring.

In the customer assistance area, more than 31,000 customer assistance contacts were handled by the Computer Center consultants, and 3,035 Programmer Trouble Reports were researched and answered.

Accurate, up-to-date technical documentation is essential for users to make the most effective use of the NIH Computer Utility. During FY84, nearly 165,000 copies of technical publications were sent to the 7,399 users registered for the Automatic Documentation Service and single requesters. The Computer Center Users Guide was updated 5 times, 4 new technical documents were published and 74 others were either revised or updated. Seven issues of *INTERFACE,* including an *Annual Index,* were published.

Changes designed to improve the performance and reliability of the operating system required the implementation of 36 SYSGENS (software reconfigurations). Nearly 7,446 fixes, both preventive and corrective, were tested and applied to the system, and 17 new releases of current software packages were installed.

The Data Base Applications Section develops and maintains the central administrative data base for NIH materiel and financial management (left to right): Jane Blessley, Martha Alliston, Shirley McAllister, Roger Dailey, Carol Richtand, and John Price.

Data Management Branch

J. Emmett Ward, Chief

In FY84 the Data Management Branch again worked on many projects involving virtually every major segment of NIH. These projects vary in size, complexity, and duration. The following summaries omit smaller efforts.

Clinical Research, Patient Care, Epidemiology

Sleep Study. Darius Georg, Peter Basa (DMB/ASPS); Wallace Mendelson (NIMH/CPB). This system has been developed to provide a computerized method for scoring sleep data. Programs to edit, update, and report on the data are being written by DMB staff to be implemented by Mr. Wallace Duncan and NIMH staff. Programs to produce reports based on 24-hour sleep periods that fall between two dates selected by the user are being developed to provide information for the research group to analyze patient sleep patterns.

Survey of Patients with Homocystinuria. Steve Soroka, Larry Martin (DMB/ASPS); S. Harvey Mudd (NIMH). Physicians from around the world who have treated patients with homocystinuria were asked to respond to a standard questionnaire about these patients. DMB wrote programs to create the computer file and to identify errors in the data. Statistical analysis will be performed by Dr. Mudd and an NIMH statistician.

BRIGHT STAT-PACK. Brian Cole (DMB/SAS); David Rodbard, Peter Munson (NICHD/BES). This computer system running on the DECsystem-10 enables Clinical Center investigators to analyze their own clinical data. A new release of BRIGHT was installed during FY84, which provides a more convenient and faster way of calling the STAT-PACK programs. Bar charts with confidence limits, the ability to produce SAS and SPSS files, and a life table statistical test were added to the features available in STAT-PACK.

Survival System. Diane Feskanich (DMB/SAS); Ardyce Asire (NCI). This life table analysis system was developed in the 1960's to support the End Results in Cancer Studies of NCI. Maintenance, improvement, and dissemination of the system is now the primary goal. During FY84 a copy of the system was sent to the Swedish Cancer Registry in Stockholm, the Ontario Cancer Treatment and Research Foundation, and to the American College of Surgeons in Chicago.

Antibody Panel Construction Program. George Roberts (DMB/SAS); James Aubuchon (CC/BB). A system was developed to construct and select panels of ascending utility from the file of blood donor phenotypes using the criteria and algorithm developed by the Blood Bank. Preliminary results of the method were presented at an international meeting early in 1984. An alternate solution that more nearly mimics the manner in which experienced humans select and rank panels was developed during FY84.

Cause of Death in Neurological Disease. Diane Feskanich (SAS/DMB); Vijay Chandra (NS/NINCDS). NINCDS epidemiologists are analyzing data in tapes from the National Center for Health Statistics providing multiple causes of death in some 14 million people who died in the U.S. between 1971 and 1978. During FY84 case-control studies were run for motor neuron disease, epilepsy and cerebrovascular disease.

Clinical Information Utility (CIU). David Blessley, Aileen Kelly, Ron Edwards (DMB,CSS). This project is an ongoing production and developmental effort that provides a comprehensive data base for research and patient care. During FY84, three new features were added:

- Retrieval Assistance Module. The Clinical Support Section performs CIU data retrieval for the NIH community. The retrieval criteria, which are written by the requestor, are defined for the CIU using this module. This permits input/output requirements and selection criteria to be defined interactively. Job Control Language statements are generated and attached to the criteria. All of these statements are submitted into the batch automatically.
- Clinical Research Information Service (CRIS). This facility was provided to the Medical Records Department to enable the electronic transmission of retrieval requests from the Clinical Center to DMB. This feature and the retrieval assistance module improve the efficiency with which CIU retrieval requests are processed.

- Test Groupings for Medical Records Department. Chemistry and hematology data are normally processed and addressed by individual test names. A procedure was designed and developed for grouping test names. This procedure permits the user to name a group of tests for retrieval.

Phoenix Clinical Information System. Aileen Kelly (DMB/CSS); Robert Baird (NAIDDK). For about 17 years, Epidemiology and Field Studies Branch and the Phoenix Clinical Research Section, NIADDK, have been conducting studies relating to the cause, diagnosis, course and treatment of diabetes mellitus. This project is being initiated:

1. to develop a master file of complete patient data by integrating data from individual studies,
2. to provide a user-defined retrieval facility, and
3. to improve existing data collection procedures.

During FY84 a system design was presented to and approved by NIADDK to accomplish (1) and (2) above. Work has begun on development of this system; its initial implementation is planned for late FY85.

Drinking and Driving. George Roberts (DMB/SAS); Alex Blumenstial, Peter Mengert (USDOT). Prespeech and postspeech questionnaires were administered to students listening to talks on drinking and driving. PL/1 programs were written to edit and recode the data and create new variables. SAS was used for tabulation and analysis. Various statistical analyses were run to determine both test reliability, and whether or not the talks had any effect on student attitudes towards driving after drinking.

Evaluation of Outpatient Chemistry Data at University of Virginia Medical Center. Dave VanSant, George Shakarji (DMB/OC); Eugene Harris (Virginia Medical School). This study involves laboratory test values of outpatients for sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, and glucose. Extensive serial correlation using F statistic from one-way analysis of variance runs was used, combined with correlation coefficients, to obtain valid results of the patient's data over time. In addition to the serial correlation analysis, other time series analyses were done on the data to ascertain consistency and accuracy of the serial correlation results.

Seasonal Affective Depression. Dave VanSant (DMB/OC); Norman Rosenthal (NIMH/CPB). During FY84, three analyses projects were completed:

1. Effects of Fall Daylight Saving Time on Seasonal Affective Disorder (SAD) Type Depression. This project consisted of investigating the effects of the fall daylight saving time change on patients with Seasonal Affective Disorder (SAD) depression. Using a scale of 1 to 24, patients rated themselves daily on energy level, anxiety, mood, tiredness, and overall feelings. For each patient, means were obtained for six one-week periods where the time change day (10/31/82) was designated as the first day of week four. A dataset of weekly means for 33 patients was input to a repeated measures analysis of variance program and to Duncan's multiple range test. The Duncan test showed that for two self-ratings, energy and mood, there was a statistically significant difference ($p=.05$) between weeks three and four but no significant difference between all other pairs of adjacent weeks (one and two, four and five, etc.). The difference consisted of a sharp drop in energy level and a worsening of mood from week three to week four. In addition, anxiety and tiredness showed an interesting increase from week three to week four, but the increase was not statistically significant.
2. Effects of Bright Light Treatment on SAD Type Depression. This project investigated the effects of a 7-day bright light treatment on mood, energy level, anxiety, tiredness, and overall feelings on a group of 16 patients with SAD depression. Using repeated measure analysis of variance and Duncan's multiple range test techniques, the study indicated that the light treatment improved the patient's overall mood significantly. However, other ratings--i.e., energy, feelings, anxiety, etc.--were not altered or were not improved significantly.
3. Effects of Holiday Periods on SAD Type Depression. This study involved evaluation of the effects of holiday periods (Thanksgiving, Christmas, New Year's, and Labor Day) on mood, energy level, anxiety tiredness, and overall feelings on a group of 36 patients with SAD depression. Using repeated measure analysis of variance and multiple range tests for each patient's data for each of the holiday

seasons, it was determined that all findings were inconclusive except for Labor Day weekend, where, as expected, the overall ratings began to worsen.

Laboratory Investigation

Biologics Protocol System. Renee Edwards and Nan Miller (DMB/CSS); Susan Preston (Bureau of Biologics). The Bureau of Biologics runs a product certification program that compares the results submitted by manufacturers to results done in-house. This comparison is done to determine whether or not products can be released to the public. The system, which is executed interactively, permits the Bureau to define data collection forms and their formats, to edit criteria for the data elements, and to retrieve data using Boolean Logic and relations.

Program Management and Administration

Administrative Data Base. Data Base Applications Section, Barry Madia, Martha Alliston, Gerald Stoner (DMB); Office of Administration, Office of Research Services (OD/NIH).

This ongoing project utilizes data base technology in support of NIH-wide materiel and financial management activities. As the ADB entered its sixth year of development and operation, much time was spent in enhancing existing software. During FY84 some 90 change control items successfully went into production. Of special note were the following accomplishments:

- the design and development of a Market Requisitioning System; the implementation of Stock Requisitioning and the Central Stores Inventory; the replacement of the self-service store system by an IBM 34 System; the implementation of a fast small purchase capability for DELPRO users; support of discount data on source agreements.
- in the Accounts Payable area, all major reports were placed on microfiche; payments now can be checked by both Employer Identity Number and Invoice number against all previous payments, thus eliminating the possibility of duplicate payments; invoices now can be tracked by line number; voucher examiners can record and retrieve disallowed dollar amounts.
- the Information Center continued to maintain the ADB history and audit files while producing the necessary periodic reports; some 50 recurring user reports were written to support stock requisitions; a study has been initiated to determine the feasibility of allowing user interaction with data bases that have been "down-loaded" to personal computers.

Human Nutrition Research and Information Management System. Judy Mahaffey, Dennis George, Mike Letke, Charlie Twigg, John Parks (DMB/ASPS); Thomas Vogl (OD). The Secretaries of Health and Human Services and of Agriculture were mandated by the Congress to establish a Human Nutrition Research and Information Management System encompassing all such research supported by the Federal Government. Specifically, Title XIV of P.L. 97-98 states as follows:

> 'SEC. 1427. The Secretary (of Agriculture) and the Secretary of Health and Human Services shall formulate and submit to Congress, within one hundred and eighty days after the date of enactment of this section, a plan for a human nutrition research management system. This system shall be based on online data support capability allowing for fiscal accounting, management, and control of cross-agency human nutrition research activities.'

To this end, the HNRIM System was designed to:

1. establish a central data base of human nutrition research and training activities supported by the Federal Government;
2. make the information in the data base available to all Federal agencies, the Congress and its staff, and to the scientific community;
3. provide online query capabilities, including free text searches on narrative information; and
4. provide reports itemizing and summarizing nutrition research activities for the fiscal year.

This system includes information on human nutrition research and research training activities supported in whole or in part by the Federal Government. Each participating agency (at present Department of Health and Human Services, Department of Agriculture, Veterans Administration, Agency for International

Development, Department of Commerce-National Oceanic Atmospheric Administration, and the Department of Defense) assembles and submits its own data. The data is validated for accuracy and completeness as it is entered onto the HNRIM data base. Error reports are returned to the agency for necessary actions. Data retrievals may be made at any time by the Agency or other interested parties. The system is currently being implemented.

System for Classifying NIH Research and Development Awards. Darius Georg (DMB/ASPS); John James (DRG/RAE). The objective of this ongoing project is to test the feasibility of using CRISP index terms for categorizing NIH research projects into basic, applied, or developmental research, and continue to develop a computer system to show percentage distribution of dollars associated with each category. New methods of calculating the distribution of research dollars are being developed and tested using the current years data to provide information to the different agencies to assist them in preparing the annual National Science Foundation (NSF) reports.

Printing and Reproduction Branch Internal Inventory Monitoring System. Peter Basa (DMB/ASPS); Reginald Russell (PRB). This system is being developed to create a data base of the Printing and Reproduction Branch's internal inventory. The system will allow efficient monitoring of their supplies by producing a current inventory report after each daily update.

Cancer Information Service. Dennis George, Charles Twigg (DMB/ASPS); Judith Stein (NCI/DCPC). The purpose of this project is to provide consolidated reports for the 24 offices of the Cancer Information Service Network. This includes annual and semiannual reports of the daily call records. During FY84 work was begun on the compilation and analysis of data for a national survey of users to the Cancer Information Service.

Worker's Compensation Monitoring and Control System. Steve Soroka (DMB/ASPS); Lucille P. Stamps (DPM). This system was developed to assist B/I/D administrators in monitoring workers' compensation usage. The system will produce reports containing compensation cost and days missed data that will be sent from the compensation office to each B/I/D.

Patient Travel Expenditures Monitoring and Control System. Steve Soroka (DMB/ASPS); Steven Groban (CC). This system was developed during FY84 to assist administrators in monitoring patient travel expenditures and to reduce the amount expended on patient travel. The system provides travel expenditure reports that are sent from the Clinical Center Outpatient Department to institute administrative offices and to various branch offices in the National Cancer Institute.

Training Information System. John Parks (DMB/ASPS); Milton Tipperman (DPM). This system was developed to help the Training Management Branch expedite data requests and management analysis of data gathered on DHHS Form 350. The system became operational during FY84. Evaluation of reporting and query needs continued.

Interferon Production Monitoring System. Peter Basa (DMB/ASPS); Hilton Levy (NIAID/LVD). The purpose of this project is to develop a system to monitor the production and subsequent use of interferon on an experimental basis. Various production techniques and use protocols are to be monitored in both human and animal subjects. Data from the clinical data base was received. Work on a graphics package was begun during FY84.

Information System of Extramural Scientists. Darius Georg (DMB/ASPS); William Rhode (OD/OPPE). This project involves the creation of a data base drawn from various sources to perform analysis of patterns of involvement in NIH science review activities by extramural scientists. The data base is continually being updated with current data and reports are being produced upon request. Currently, the system to update the OPPE Management Data Bank File is being modified to make collection of data and updating of files more efficient.

Employee Health System and Accident Reporting System. Steve Soroka (DMB/ASPS); Julio Rivera, John Leach (ORS/S). A system was developed in FY83 to combine the employee health and accident reporting systems. During FY84, a new query facility was installed to replace the SLR query. The new query offers a more flexible output format and is less expensive to run.

Visiting International Scientists in America MIS (VISA). Penny Brogan (DMB/ASPS); Libby Low (FIC). This system provides information on foreign scientists who are in the U.S. to perform health research. Most of these scientists are working at NIH. The system has been operational for several years. It provides monthly and yearly reports to NIH administrators and to foreign embassies. Important new features added this year include:

1. Program modification to allow the Institute list to be produced for either Visiting or non-Visiting Program scientists;
2. Modification to the selector program to allow selection of scientists based on a minimum number of days on duty during a given time span.

NCI, RAEB Grants/Contracts Information System (GENIUS). Penny Brogan (DMB/ASPS); Harry Canter (NCI/DRCCA/RAEB). The Grants Elemental Network Internal Users System (GENIUS), operated by the Research Analysis and Evaluation Branch of DEA, NCI, is the official NCI programmatic information system. The system, initiated in 1973, has been enlarged and maintained in an ongoing fashion. It provides both administrative and scientific classifying information via six subsystems: grants, contracts, intramural projects, unfunded grants, grant-supported literature, and radiation grants/contracts. Enhancements this year included a complete revision of the grants/contracts subsystem.

Computer-Assisted RIF System. Brian Cole (DMB/SAS); Nelson Sparks, Lynn Gentile (OD). All government agencies must put an automated RIF system in place. During FY84 the procedures for rank-ordering NIH employees with respect to retention priority were developed and programs written. A preliminary list has been produced.

Workload Management System for Nurses. George Roberts (DMB/SAS); Major Deena Norton (Walter Reed). The WMSN is designed to provide a patient classification system and to quantify these classifications into care hours and nursing/hospital sites. Mr. Roberts supplied programs for collecting and editing data and for analyzing the system.

Study of FY77 Principal Investigator Characteristics. George Shakarji, Dave VanSant (DMB/OC); Dr. Stuart Wright (DRG). This study assesses the characteristics of all investigators active in FY77 project grants. FY84 evaluations were made comparing key variables such as Institute and activity, Institute and kind of research, Institute and age, Institute and sex of principal investigators, Institute by degree, and age by degree.

Study of FY77 Subproject PI's. Dave VanSant, George Shakarji (DMB/OC); Dr. Stuart Wright (DRG). This study examined the characteristics of a nine percent sample of all project principal investigators active in FY77 grants, and compared them with regular principal investigators active in the same year with respect to Institute, activity, sex, and degree. As a result of the analysis, NIH decided to sponsor a second and more complete study not only of project sub-PI's but also of all other research professionals involved in multiproject grants.

Evaluation of Personal Characteristics and Training of Grant Recipients. George Shakarji (DMB/OC); Dr. Stuart Wright (DRG). Statistical examination of personal characteristics and training continued this year of all principal investigators who were awarded their first grant in FY72 and the results were compared to their subsequent success at NIH thru FY80. All descriptive data have been evaluated and multivariate analyses have been conducted on variables of training and personal characteristics with respect to measures of success. Additional appropriate variables and their weights to the final outcome are being evaluated. Because of the massive number of variables involved in the study, the project may continue for some time before the analyses are concluded.

Biomedical Communications Applications

Selective Dissemination of Information. Mary Lee Dante (DMB/SAS). SAS continued its support of the current awareness search requirements of NIH.

Chemical Biological Activities (CBAC) was dropped and DCRT processing of BIOSIS tapes was dropped in favor of a new, personal computer-based system from Biosciences Information Service (BIOSIS). The new service includes both hard-copy printouts of hits, based on the scientists' personal interest profiles (C.L.A.S.S.), and a floppy disk containing those hits which can be used to build a personal data base for use on a choice of several personal computers (B.I.T.S.).

Computer Research and Technique Development

Chemical Macromolecules. Sigurd Knisley (DMB/SAS); Richard Feldmann (OD/DCRT). In FY84 the Apollo system replaced the PDP-11/Evans and Sutherland Picture System/Conrac Frame Buffer Complex. Programs for the three-dimensional shaded surface molecular display were converted, rewritten, and enhanced for use on the new system.

RMAG Products Support. Bob Magnuson (DMB/OC). Support was provided for RMAG, SLR, Logic Subroutines, Arithmetic Subroutine, SLANG, PDOC, CP Tools, and SFOR. This support included software maintenance, customer assistance, and the teaching of formal DCRT courses. In particular, a special effort had to be mounted to change over to the new NIH 8188 terminal from the old NIH 7000.

SASM: A Structured Programming Macro Library for the IBM PC Assembler. Bob Magnuson (DMB/OC). Designed to assist IBM PC Macro Assembly Language programmers, the SASM structure macros generate block-structured programs. The generated blocks can be nested to whatever level required.

IBM Personal Computer Support. Bob Magnuson (DMB/OC). In support of the personal workstation project, support is provided for the introduction and use of the IBM PC. Included are hardware component selection and testing, software creation, maintenance and evaluation, and the teaching of formal DCRT courses.

The Computer Systems Laboratory provides computer support for Flow Cytometry/Electronic Cell Sorters in several laboratories. CSL electronics engineer Ronald Fico (left) works on one of the advanced systems with NCI biologist David Stephany.

Computer Systems Laboratory

Alan M. Demmerle, Chief

Clinical Research, Patient Care, Epidemiology

Computer Support for Flow Cytometry/Electronic Cell Sorters (FC/ECS) (NCI, NHLBI, NIAID). This project now directly supports computer systems for the acquisition, display, and analysis of data from: eight FC/ECS instruments in three NIH Institutes; one system in another government agency (CDC); and indirectly supports three systems in three private sector laboratories. Four systems use the RT-11 operating system to process data from one user at a time. The more advanced versions use the RSX-11M operating system to support multiple users and tasks simultaneously.

This year the advanced version, designed for high volume, was installed first as an upgrade to the FC/ECS in the Immunology Branch, NCI, and subsequently has been installed at other sites. This system features an LSI-11/23 microcomputer (satellite) that connects to an 11/24 minicomputer (host) via an interprocessor link. A FC/ECS operator interacts with the satellite for parameter entry and data acquisition, which is performed independently of the host. The host stores, displays, and analyzes the data, and prints or plots the results. This system also features the ability to connect commercially available FC/ECS computer systems to the RSX/CSL (host) for purposes of data transfer, storage, and/or analysis.

Cardiac Scintillation Probe (CC, NHLBI). This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catheterization, permits simultaneous quantification of the variation of LV volume and pressure. The system can continuously derive parameters such as LV compliance, ejection fraction, filling and ejection rates, and various temporal relationships.

In 1984, the probe continued to be used in intervention studies in the catheterization laboratory, NHLBI, on patients with asymmetric septal hypertrophy and coronary artery disease. A second probe is being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit of the Clinical Center.

Nuclear Medicine Computer Systems (CC). CSL has continued consultation and support for imaging systems in the Nuclear Medicine Department to assess their changing needs and to evaluate their increased requirements with a view toward their anticipated growth. This year, the requirements for a new department-wide computer system were specified and a Request for Proposals to acquire the system was written.

The computer processing requirements for Nuclear Medicine are projected to grow 10- to 30-fold over the next few years due mainly to increases in the number of tomographic type studies. The new department system will handle the present requirements and will allow for expansion to accomodate the projected growth. It is anticipated that this system will be a node on the proposed Clinical Center Picture Archival and Communication System.

Medical Intensive Care Unit Patient Monitoring Computer System (CC). Patients in the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data display, and feedback control, as required in support of patient care and research protocols.

The facility also contains a state-of-the-art catheterization laboratory with flexible computerized physiologic monitoring features, and a high resolution x-ray system with digital subtraction angiography capability. Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

A nonimaging cardiac probe was interfaced to the software development system in FY84. The probe provides left ventricular volume data by counting scintillations, after the administration of an injected radioisotope. Development of data analysis software, markedly different for this probe than for the one in the NHLBI catheterization laboratory, continued this year and a clinical evaluation period was initiated.

Automated ECG Processing (CC). The Clinical Center's Heart Station was automated in FY81 with a computer system that provides online acquisition, analysis, storage, and retrieval of diagnostic electrocardiograms. The newest versions of the vendor's turnkey software has been in routine clinical operation for over two years.

As utilization of this system has progressed, the medical staff has been identifying specific diagnostic criteria and statements that require modification to provide compliance with NIH Heart Station standards for diagnostic electrocardiography. During FY84, CSL assisted the vendor in correcting minor software problems.

Department of Rehabilitation Medicine Computer System (CC). This project involves the development of computerized instrumentation techniques in collaboration with the Department of Rehabilitation Medicine, NIH Clinical Center. Techniques are being implemented to acquire anatomical and physiological information from patients, to perform required calculations on the data obtained, and to display necessary results to the medical staff.

The techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System will provide these measurements. The computer part of the system will allow the medical staff to enter additional data into a data base using computer-generated forms displayed on a terminal screen, and to make inquiries and generate reports.

In FY84, the purchased system was installed in a temporary location of the Clinical Center while renovations for the final laboratory location were completed.

Picture Archiving and Communication System (PACS) (CC). The purpose of this project is to develop a system to store and transmit medical images, and to allow access to pictures representing different imaging modalities at the same viewing station. Such a system will draw on the latest technological developments in data storage, image display, and data communications. The system will reduce the amount of time required to obtain images for clinical review, and also will facilitate research by making population and cross-modality studies more feasible. Based upon a study performed last year by CSL, the Clinical Center has requested PACS funding for FY86. This suggests a detailed design effort in late FY85 or early FY86.

Automated Management of Critically Ill Patients (CC). This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is to use computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is used in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Current project focus is on cardiovascular disorders that give rise to low output syndrome. Several alternative methods for closed-loop automated medical interventions are being investigated.

During FY84, software which models the drug administration protocol and the three major subsystems accounting for drug action on a cardiovascular function have been completed. Preliminary model studies indicate an instability in the cardiovascular dynamics model, due to inadequacies in the analytic expressions for the forcing functions representing myocardial contractility.

Computer Interfaces for Clinical Laboratory Instruments (CC). CSL designs and implements microprocessor-based systems to aid in automating functions in the Clinical Pathology Department, CC. In previous years systems were developed for automated cell counters and the entry of hematology morphology data.

This year we completed the implementation of an extension to the hematology morphology system. A total of eight user stations now are available for online white cell differential counting. This year we also started work on a new online entry system for urinalysis data in the Clinical Chemistry Service.

Anesthesia Computer System (CC). This project is a collaborative effort between CSL and the Anesthesiology Service, CC, to develop improved computer-based instrumentation techniques and to identify and investigate ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room and on a greater use of noninvasive monitoring methods.

This year, work on a preliminary system design was completed, and development of a monitoring and reporting system for the operating room began. Initial system testing is anticipated during the fall of 1984. A respiratory monitoring system composed of a microcomputer and a mass spectrometer gas analyzer also was developed this year to let anesthesiologists monitor inhaled and exhaled gas concentrations in the operating room.

Medical Information Technology Project. This project is concerned with the development ot better ways to automate the essential physician contribution to the health care record. In this third year, in collaboration with a practicing dermatologist and a gastroenterologist, we are field testing an ambulatory patient care treatment system. It is designed to help the physician generate patient information and treatment schedules, pharmacy prescriptions, medical and surgical reports, laboratory test requests and results, and referral letters to other doctors.

Physicians interact with the system using high-speed user-friendly menu selections with many preselected default fields. The clinical software, table driven on a microcomputer, is being streamlined for use in various clinical care and research environments.

Biomedical Image Analysis Projects (CC). CSL would like to develop general-purpose algorithms and techniques for image input, image enhancement, feature extraction, three-dimensional representation, image reconstruction, and other techniques of image processing and image reconstruction. We have found the best way to do this is through collaborative efforts with a number of NIH researchers who encounter a relatively similar class of problems in unique, individual settings.

Currently we are working on a project for cardiac ultrasound image processing, which is directed towards providing the NIH Clinical Center Medical Intensive Care Unit with the ability to assess cardiac function via computer analysis of ultrasound images of the heart.

An extensive review of earlier work has led to the development of design criteria for an interactive image processing methodology for the estimation of ventricular ejection fraction. A hardware/software link exists between the ultrasound system and the remote computer. Applications programs written by CSL currently are being tested.

Automatic Coronary Venous Flow Measurements (NHLBI). CSL started collaboration this year with the Cardiology Branch, NHLBI, to develop a microcomputer-based system to automate coronary venous blood flow measurements.

This system acquires signals derived from a triple-thermistor-tipped catheter in realtime, and then computes blood flow from these signals. The system will improve the accuracy and speed of blood flow measurements used by the Cardiac Catheterization Laboratory in a variety of clinical procedures; the computer will replace the need for manual graph extrapolation and for hand calculations currently used.

Speech Analysis System (NINCDS). CSL is assisting the Communicative Disorders Program (CDP), NINCDS, in implementing a computer system for acquiring and analyzing speech and motor signals from patients with speech impairments. CDP has identified a software package called MITSYN that can perform all required functions, and CSL has specified a computer system (an LSI-11/73) with analog I/O peripherals on which this package will be run. When the ordered equipment and software are delivered, CSL will integrate the system components, install the operating system software, and write the signal record/playback software required to interface MITSYN with the analog I/O devices.

Laboratory Investigation

Molecular Modeling and Sequence Analysis (NIADDK, NCI, Rockefeller University, Boston University). The sequence of some regular proteins, when correlated with other structural information, can be utilized to evaluate models of protein or polymer structure. CSL participates with other institutes in this work by applying computer techniques, including Fast Fourier Transform techniques, to the correlation analysis of protein sequence data.

This work includes the development of software for the generation of linear sequence maps. Current studies involve: the sequence analysis of keratin and other intermediate filaments (with NIADDK, NCI); computer simulations of the effects of staining for helical proteins such as actin (with NIADDK); sequence analysis of streptococcal M5 protein (with Rockefeller University); and computer models of branched polymers (with PSL, DCRT).

Image Analysis of Chemical and Biochemical Systems (NIADDK, DRS, NCI, NICHD, Brookhaven National Laboratories). CSL is active on several projects aimed at the processing and analysis of biochemical images. One goal is the simplified and accurate quantitative analysis of one- and two-dimensional gels. New software is being developed by CSL to utilize the features of the new image processing facility, and to more easily and quickly analyze gels, autoradiographs, and hybridization experiments.

A new virus structure, Vesicular Stomatitis Virus (VSV), currently is being studied. The structure was determined by image processing of conventional electron micrographs as well as Scanning Transmission Electron Microscopy (STEM) data. In addition, a new method has been developed to perform radial reconstruction on STEM projections of cylindrically symmetrical macromolecules. During FY84 this method was applied to Tobacco Mosaic Virus as a test case.

Electron Microanalysis Facility (DRS). CSL is collaborating with BEIB, DRS to develop an automated electron microanalysis facility consisting of two electron microscopes interfaced to a PDP-11/60 computer system. The facility is being used for research into the elemental composition of biological specimens and for the development of new techniques in electron microscopy.

CSL designed and implemented the computer system, which acquires and displays the spectra and images resulting from Electron Energy Loss (EEL) and x-ray spectrometry. This year, the image display capabilities of the system were enhanced, and a technique called "r-imaging," which improves the quality of EEL images, was developed. The system was used on several new and ongoing biological research projects.

Californium-252 Plasma Desorption Mass Spectrometer Data System (NHLBI). This instrument provides NIH the capabilities of mass analysis for compounds difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000. The process of software verification and reorganizations, begun last year, now is in its final stages.

Studies were begun on the nature of the ionization process, utilizing our capability to record each new ionization event for further study. Computer system memory was expanded to 1024K bytes. Modifications were made to the mass spectrometer ion source to enhance resolution, permit both negative and positive ion spectroscopy, and improve safety and reliability. Electronic monitors also were installed to prevent catastrophic system failure in the event of vacuum and/or power loss.

Distributed Laboratory Data Acquisition and Control System (DLDACS) (NIADDK). A Distributed Laboratory Data Acquisition and Control System, DLDACS, has been implemented for NIADDK, in Building 2. The system consists of a network of remote microcomputers connected in a star configuration through a communications processor to a central processing computer. The remote microcomputers handle all of the realtime data acquisition requirements and provide instrument control functions when required. Currently there are 9 satellites connected to the system supporting 11 instruments.

During the past year sample temperature control was added to several LDACS and software to perform kinetics, melting runs, and multiscan averaging was developed for the CARY 210 spectrophotometer. APR, a program for data analysis, was improved significantly.

Personal Computers in Laboratory Application (DCRT). Personal computers have become a viable alternative to assembling board-level microcomputer systems for many laboratory applications. They offer a substantial "head start" and form the basis for programmable acquisition and control systems.

This year we evaluated several laboratory interfacing hardware and software products so that we can assist users in configuring systems for laboratory applications. The results of these evaluations were applied to several projects described elsewhere in this report; projects for which we provided only advice are not described here.

Data Acquisition System for UV Spectroscopy (NCI). A data acquisition system was developed to collect data from a spectrophotometer, to transfer this data to the DCRT computer facility, and to facilitate analysis of the data emulating a graphics terminal.

The system is based on a Digital Equipment Corporation MICRO/PDP-11 microcomputer that is interfaced to a Cary Model 118 Ultraviolet Spectrophotometer. This computer controls the spectrophotometer's monochrometer through a custom interface. Absorbance data is acquired from the instrument and stored locally. At a convenient time the stored data is transferred to the DCRT facility where analysis is performed by using the MLAB program. This system assists the analysis by emulating a graphics terminal that is compatible with MLAB. This system was started and completed during 1984.

X-Ray Diffraction Studies of Muscle Tissue (NIADDK). The Computer Systems Laboratory is assisting the Laboratory of Physical Biology (LPB), NIADDK, in interfacing a computer system to a two-dimensional x-ray detector to be used for x-ray diffraction studies of muscle tissue. The computer system is a Masscomp 500 series, which is based on the Motorola 68000 microprocessor and runs the UNIX operating system. This computer is particularly well-suited to high-speed data acquisition applications, and CSL was therefore interested in gaining experience with it. Two computer systems were purchased and installed in FY83; the LPB system in July, and the CSL development system in September.

This year CSL designed and implemented the data acquisition software acquisition hardware. Software to analyze the x-ray diffraction patterns was designed and implemented by LPB. We are currently awaiting delivery of the detector by a contractor, who has encountered many difficulties in design and fabrication. We hope that development of the detector will be successful and that the system will be put into production use early next fiscal year.

Program Management And Administration

Library Automation (DRS). Since FY79, CSL has provided technical consultation to the NIH Library. As automation has proceeded in the library, CSL has provided a requirements study, a market survey, a cost benefit analysis, programming assistance, and technical support in contract negotiation. As the introduction of microcomputer technology is making more extensive library automation cost effective, CSL, during FY84, has extended its technical support to the smaller DCRT Library.

As a result of CSL efforts, the NIH Library has purchased a turnkey library system that will support an online catalog and automated control of circulation, acquisitions, and serials. This year, CSL also has assisted both the NIH and DCRT Libraries to optimize their use of computers including the evaluation and implementation of solutions involving purchased turnkey systems, microcomputer-based office automation systems, and the sharing of resources between libraries.

Biomedical Communications and Conference Support

Computers in Cardiology Conference. CSL continued its support of the annual *International Conference on Computers in Cardiology.* The Conference provides a forum for direct interaction and exchange between physicians, computer scientists, and engineers who are involved in various aspects of clinical computer systems in the field of cardiology.

CSL Consulting

This year, as in past years, CSL provided consultative assistance to several intramural and extramural program areas.

- CSL assisted DRS in monitoring contractor performance on the development of the Small Animal Data Management System for which CSL previously prepared the RFP.
- A CSL staff member began a two-year term on a standing committee for evaluation of NCI-proposed intramural support contracting.
- Two activities reported in prior years as collaborative projects with NHLBI (*Potentiometric Titration Controller* and *Metabolic Energy Measurements*) were continued as consulting efforts for a second year with CSL providing only occasional microcomputer technical advice to NHLBI investigators.
- Technical consultation on the DEC RSX-11M operating system was provided to ten investigators representing five NIH Institutes and two organizations outside NIH.
- CSL helped NCI's Development Therapeutics Program monitor a contractor's performance in the development of a work station for computer entry of chemical structure data.
- CSL helped an investigator at NIADDK's Phoenix Clinical Research Station select and configure a data acquisition system to record measurements in a human calorimetry room.
- CSL provided assistance to DMB to connect a digital cassette tape unit to an IBM PC so that data acquired by Radiation Counter Data Loggers can be played back to the PC for analysis.
- Two services were provided for Flow Cytometer/Electronic Cell Sorting (FC/ECS) sites. One was for technical assistance and guidance for a an FC/ECS computer system at the Uniformed Services University of the Health Sciences. The other service was provided to the Centers for Disease Control, Atlanta, Georgia, to help install CSL's new FC/ECS software.

Computer Research And Technique Development

Image Processing Facility (DCRT). This project provides NIH investigators with the means to digitize, analyze, and display a variety of biomedical images. The system consists of a powerful 32-bit computer with medium- and high-resolution displays. A very high resolution microdensitometer allows precise digitization of images acquired from a variety of sources (e.g., electron microscope). The system was completed this year with the addition of two more user stations, and an online connection to the microdensitometer.

Medical Image Data Compression (DCRT). This project involves reducing the number of information carrying units used to represent a medical image, in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques that will be suitable to the clinical environment are being investigated.

During FY84, the entropy of digitized x-rays and computed tomography images was calculated in order to obtain a theoretical bound on the maximum compression ratio obtainable with noiseless techniques. These techniques have shown a limit of approximately 2:1 compression. In addition, Hadamard transform methods, which offer far greater compression at the cost of loss of fidelity, are being programmed and evaluated.

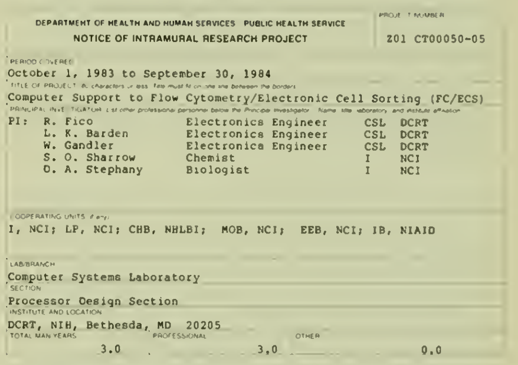
Integrated Input/Output (DCRT). The Integrated Input/Output project is an attempt to expand the user interface of a personal computer from the usual keyboard input and CRT display to include more friendly and efficient modalities of communication.

CSL efforts on this project include the development and modification of hardware and software to support desirable interface features such as speech recognition and voice response, bar code interpretation, touch-sensitive CRT screens, and graphics input devices. In the first phase of this project, a prototype voice input personal computer system was developed for use by a handicapped DCRT employee.

DCRT Local Area Network (LAN) (DCRT). In recognition of the increasing importance of local area networks (LAN's) in laboratories, hospitals, computer facilities, and offices, CSL is planning a network for DCRT. Two goals led CSL to undertake this project. First, we thought it important to develop expertise in LAN technology so that we will be able to offer competent advice to other NIH organizations in the future. Second, DCRT has some 40 IBM PC's, plus numerous other terminals, modems, and computer systems that can benefit from interconnection by a LAN.

We have selected the Ethernet LAN because it is an established standard supported by products from a broad spectrum of companies. This year, we planned an Ethernet for Building 12A, with the expectation of installation in the fall of 1984. We may extend the network to Buildings 12 and 12B during FY85.

Research Projects



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00050-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT
Computer Support to Flow Cytometry/Electronic Cell Sorting (FC/ECS)

PRINCIPAL INVESTIGATOR

PI:	R. Fico	Electronics Engineer	CSL	DCRT
	L. K. Barden	Electronics Engineer	CSL	DCRT
	W. Gandler	Electronics Engineer	CSL	DCRT
	S. O. Sharrow	Chemist	I	NCI
	O. A. Stephany	Biologist	I	NCI

COOPERATING UNITS (if any)
I, NCI; LP, NCI; CHB, NHLBI; MOB, NCI; EEB, NCI; IB, NIAID

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
3.0	3.0	0.0

Computer Support for Flow Cytometry/Electronic Cell Sorting (FC/ECS)

This project provides computer support for two Coulter MDADS, one Becton-Dickinson (B-D) FACS IV and four B-D FACS II FC/ECS instruments. High sample throughput, from data acquisition to data display and analysis, is the principal system feature. Currently, there are two versions of data acquisition and analysis systems developed and supported by CSL for the Cell Sorter Community at NIH. One version uses a single computer that runs under the RT-11 operating system. Another version, referred to as the RSX system, uses at least two computers.

A host computer, a Digital Equipment Corporation (DEC) 11/24, is used to analyze and store data. One or more satellite computers acquire data from the instrument and are connected to the host through a hardware link. The RSX system offers multiuser and multitasking support, improved recordkeeping facilities, and enhancements for data acquisition and data analysis. An RSX system was installed at the Immunology Branch, NCI, in the first quarter of FY84; the Immunobiology and Immunochemistry Branch, NIAID, in the second quarter of FY84; and the Centers for Disease Control, Atlanta, Georgia, in the third quarter of FY84.

Background and Objectives: Since FY75 CSL has provided engineering, system integration, and software support necessary to meet the data acquisiton, data display, and analysis needs of several investigators using FC/ECS instruments at NIH. Software development and testing is done on a DEC PDP-11/24 computer system owned by CSL. This allows investigators to have full use of their systems while new software is being developed.

Both the RT-11 and RSX systems allow data collection of multiple parameters on individual cells. Typically these are forward and side light scatter and various fluorescence frequencies. The data can be collected in single parameter or correlated dual parameter modes. Data analysis and display programs allow the experimenter to produce various statistics and hardcopy displays from the acquired data. The displays include three-dimensional pictures, contour maps, and vertical slice sections.

Progress in FY84: The major effort in FY84 was continuing the development of the RSX-11M system. The RSX system was developed for I, NCI, in order to provide support of current and anticipated workloads including sophisticated data acquisition and recordkeeping functions. This system is available to other NIH FC/ECS sites as required.

The new data acquisition system environment consists of a PDP-11 host computer running RSX-11M and one or more satellites connected to the host via a hardware link.

Data acquired by a satellite is sent over the link and stored at the host site. Together, the host and the satellite link software provide file transfer capability.

The development of the link software for the NIH-designed LSI-11 satellite was completed in FY82. The acquisition hardware and software of the LSI-11 system was tested in the second quarter of FY83. The RSX satellite is designed to collect up to four single parameters simultaneously with one correlated dual parameter pair, or it can collect up to two simultaneous correlated dual parameter pairs. In FY84 a feature called auto-acquisition was added to this satellite. This allows the operator to prescribe acquisition parameters independent of acquisition. The parameters are stored in a file and recalled at the time of acquisition, thereby saving the operator the tedium of entry during acquisition.

A conversion program (CONVERT), written and tested in the first quarter of FY84, converts data files collected under the old RT system to formats acceptable on the RSX system. This program automates the conversion process to a high degree and eases the transition from the older RT system to the newer RSX system.

Cell Cycle analysis programs, used for DNA research, are now available on the RSX system. In the first quarter of FY84, Cell Cycle analysis programs were acquired from the Lawrence Livermore Laboratories and adapted by CSL for use on its FC/ECS RSX-11M host. They have been rewritten to operate with the Tektronix 4025 terminal as well as the 4010 series terminals. These programs have been tested with DNA data and show satisfactory results.

During the second quarter of FY84, software and hardware were developed to connect Coulter's Multi-Data Acquisition and Display (MDADS) computer to the RSX host. The MDADS collects data from Coulter's EPICS V flow cytometer. The connection is via the MDADS high-speed parallel port. Data collected from the EPICS V is stored as files on the MDADS and subsequently transferred to the RSX host where they are converted to the RSX/CSL data format, stored, and analyzed.

CSL has also responded to many external requests and has provided copies of the interface hardware schematics, software, and documentation to FC/ECS sites in the U.S., Australia, and Europe.

Proposed Course: In the forthcoming year, CSL plans to continue development of the RSX system for both analysis and acquisition. The cell cycle analysis programs will be enhanced by incorporating software to generate plot files compatible with the RSX host zeta plotter software package. Plans to connect a Becton-Dickinson FACS IV and FACS Analyzer/Consort-30 to the 11/24 have already begun and the development will continue into FY85. Preliminary discussions and design sessions for a new CSL interface have taken place; development and fabrication will take place in FY85. The present interface is limited to four simultaneous parameters and can not easily be expanded. CSL will also continue to maintain the RT-11- and RSX-based FC/ECS sites at NIH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00051-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Cardiac Scintillation Probe

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H. G. Ostrow	Electronics Engineer	CSL	DCRT
	S. Bacharach	Physicist	NM	CC
	M. Green	Physicist	NM	CC
	R. Bonow	Cardiologist	CB	NHLBI
	D. Rosen	Cardiologist	CB	NHLBI

COOPERATING UNITS (if any)

LAB BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.25	0.25	0.0

Cardiac Scintillation Probe

CSL has continued the development of its Cardiac Scintillation Probe System begun in 1977. The cardiac scintillation probe is a transportable device used to noninvasively monitor left ventricular function. The system uses Nuclear Medicine ECG-gated scintigraphic techniques and consists of a small detector and microcomputer system mounted on a cart.

This nonimaging ECG-gated scintillation probe, when used in conjunction with left ventricular (LV) catherization, permits simultaneous quantification of the variation of LV volume and pressure. By simultaneously measuring LV volume and LV pressure, parameters such as LV compliance can be continuously monitored, in addition to such measurements as ejection fraction, filling and ejection rates, and temporal relationships.

This year the probe continued to be used for intervention type studies in the catheterization laboratory. The probe is also being used to monitor the left ventricle performance of patients in the Medical Intensive Care Unit. The pressure-volume relationships produced by the probe system allowed the effects of drugs to be quantitated in a manner not previously possible. Development is continuing on increasing the detection efficiency of the probe and in quantifying the limitation of the technique.

Background and Objectives: The development of the cardiac scintillation probe is a continuation of CSL's collaboration with the Nuclear Medicine Department, CC, and the Cardiology Branch, NHLBI. Originally this collaboration resulted in the development of a noninvasive cardiac imaging technique known as ECG-gated scintigraphic angiography using a scintillation camera. However, if the images are not required, then a time-activity curve of the left ventricle could be generated by a much smaller and simpler system.

In 1977 CSL began the development of a cardiac scintillation probe system, using a small NaI detector and microcomputer system. This system produces a time activity curve (LV volume curve) that can be used to calculate various parameters of cardiac function such as ejection fraction, peak ejection rate, peak filling rate, and temporal relationships. The system is easily transportable and allows continuous monitoring of cardiac function at the bedside or other locations in the Clinical Center outside the Nuclear Medicine Department.

Methods: The system consists of a three-inch diameter NaI scintillation probe, probe electronics, microcomputer system, and display. The system is programmed to acquire scintillation data, to process the data, and to plot and display various parameters of left ventricular (LV) function. This nonimaging, ECG-gated probe, when used in conjuction with ventricular catheterization, permits simultaneous quantification of the variation of LV volume and LV pressure. Parameters such as LV compliance can be continuously monitored. In the catheterization laboratory, pressure-volume measurements are used to study the effects of drugs on patients with various heart diseases.

Progress in FY84: This year the probe continued to be used in the catheterization laboratory to study the effects of nefidipine and verapamil on patients with coronary artery disease. In addition, the probe is being used in other intervention protocols to determine the effect on left ventricular function. The data acquisition and most of the processing is now being performed by personnel from the Nuclear Medicine Department. The order for a Hewlett-Packard computer system to replace the Intel microcomputer system was delayed but will be completed this year. The Hewlett-Packard computer will accomodate new requirements for the probe system and will be compatible with the existing analysis software available in the Nuclear Medicine Department.

The application of the probe in the Medical Intensive Care Unit, CC, is continuing to be investigated. Data acquisition and display software for the probe, which runs on the MICU Hewlett-Packard system, was implemented and tested. The probe will be used to continuously monitor left ventricular function at the bedside.

Significance to Biomedical Research: Nuclear Medicine techniques provide a relatively noninvasive procedure to assess left ventricular function. The cardiac scintillation probe permits this capability to be used for clinical research studies at the bedside and in the catheterization laboratory. The pressure-volume relationship produced by the probe system allows the effects of drugs to be quantitated in a manner not previously possible.

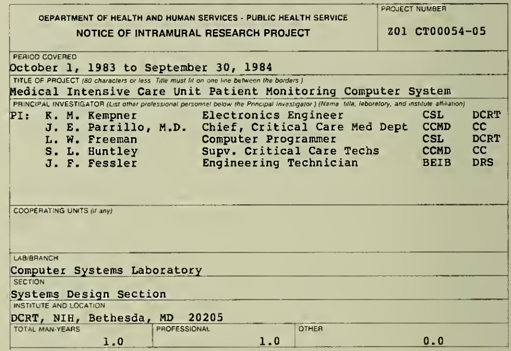
Proposed Course: Development activities in response to new applications are expected to continue. The delay in acquiring the Hewlett-Packard computer system, postponed the effort to make the probe and camera systems more compatible. Making the system compatible to the extent possible will reduce the resources required to support the probe system and will allow new capabilities developed for the camera systems to be implemented quickly on the probe system.

Publications and Presentations:

Bacharach, S., Green, M., Parentesis, P., Sindelar, A., Bonow, R., Ostrow, H., and Larson, S.: Underestimation of Cardiac Diastolic Parameters Using High Phase Reconstruction. *J. Nucl. Med.* 25: 30, 1984.

Betocchi, S., Lesko, L., Ostrow, H., Bonow, R., Cannon, R., Watson, R., and Rosing, D.: Nifedipine Concentration and Hemodynamic Effects in Patients With Hypertrophic Cardiomyopathy. American College of Clinical Pharmacology Conference, 1984.

Bonow, R., Ostrow, H., Cannon, R., Lipson, L., Maron B., Kent, K., Bacharach, S., and Green, M.: Effects of Verapamil on Left Ventricular and Diastolic Function in Patients with Hypertrophic Cardiomyopathy: Pressure Volume Analysis with a Nonimaging Scintillation Probe. *Circulation* 68(5): 1062-1073, 1983.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00054-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Medical Intensive Care Unit Patient Monitoring Computer System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. M. Kempner	Electronics Engineer	CSL	DCRT
	J. E. Parrillo, M.D.	Chief, Critical Care Med Dept	CCMD	CC
	L. W. Freeman	Computer Programmer	CSL	DCRT
	S. L. Huntley	Supv. Critical Care Techs	CCMD	CC
	J. F. Fessler	Engineering Technician	BEIB	DRS

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

Medical Intensive Care Unit Patient Monitoring Computer System

The dynamic events occurring within the Clinical Center's Medical Intensive Care Unit are monitored by a unique multiple-computer system. Capabilities of the system include online data acquisition and analysis, medical recordkeeping, tabular and graphical data displays, and feedback control, as required in support of patient care and research protocols. Elements include a minicomputer-based Patient Data Management Subsystem, a Software Development Subsystem, and a Medical Mass Spectrometer Subsystem.

The facility also contains a state-of-the-art catheterization laboratory that includes a flexible computerized Vascular Research Subsystem, with physiologic waveform processing features, and a high resolution x-ray system with digital subtraction angiography capability.

Of primary interest is the utilization of the Medical Intensive Care Unit's computer systems in the study of the etiology and therapy of septic shock.

Background and Objectives: The Medical Intensive Care Unit (MICU), administered by the Department of Critical Care Medicine in the NIH Clinical Center, receives critically ill patients from clinical programs of NIH. The MICU comprises a five-bed ward area, a pair of isolation beds, and a vascular research laboratory. The research goals of this unit include the development of techniques for automated patient monitoring and noninvasive measurements of the cardiovascular and respiratory systems. In addition, catheterization studies are performed as necessary to obtain data that are available only through invasive methodology.

Working with Clinical Center staff, CSL contributed to the engineering design of the intensive care unit. CSL also undertook the specification, procurement, and installation of the bedside patient monitoring equipment and the six computer systems:

1. a Patient Data Management System used for automatically monitoring patient variables, manually entering patient data, retrieving information online, and keeping medical records;
2. a Vascular Research Subsystem used for acquiring and processing cardiovascular pressure waveforms, measuring cardiac output, displaying measured results online, and generating a cardiac catheterization report;
3. a Software Development Subsystem used for developing software for the above described systems;
4. an Ultrasound Imaging Subsystem used to allow the visualization of intracardiac structures via multiformat displays and to facilitate the detection of structural abnormalities and other cardiac defects;
5. a Medical Mass Spectrometer Subsystem used for monitoring both the patient airway gases and the gases delivered by the patient's respirator at all seven MICU beds; and
6. a Pulmonary Function Testing Subsystem used to calculate parameters such as vital capacity and lung volumes, and to generate flow-volume loops.

The first four systems were purchased from the Hewlett-Packard Corporation and all use identical minicomputers. The Chemetron Corporation manufactured the microcomputer-based mass spectrometer system. The Collins Corporation designed and manufactured the microcomputer-controlled Pulmonary Function Testing Subsystem.

Major Findings: The automation of the MICU has aided the medical staff by managing the large amount of data needed for the care of the critically ill patient, performing desired calculations, and allowing measurements that would not otherwise be possible.

Progress in FY84: A nonimaging cardiac probe was interfaced to the software development system in FY83. The cardiac probe provides left ventricular volume data by counting gamma ray-induced scintillations, after the administration of an injected radioisotope. Data analysis software development continued this year, and a clinical evaluation period was initiated.

The cardiac ultrasound imaging subsystem's interface to the software development subsystem was completed. This opens the way for the implementation of experimental algorithms for the processing of cardiac ultrasound images. The software development subsystem's memory size was increased to facilitate the cardiac ultrasound and nuclear medicine studies that are carried out on this subsystem.

Proposed Course: Future efforts will center on hardware and software modifications necessary to enhance the system's ability to support patient care and research protocols. Possible modifications to the primary Patient Data Management Subsystem include the addition of urine output measurement scales and the computerization of fluid infusion therapy utilizing existing microprocessor-controlled infusion pumps.

Presentations:

Kempner, K.: Computers Within the Critical Care Unit. The 19th Annual Meeting of the Association for the Advancement of Medical Instrumentation. April 14-18, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00081-04

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Rehabilitation Medicine Department Computer System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. L. Martino	Electronics Engineer	CSL	DCRT
	D. C. Carpenter	Electronics Engineer	CSL	DCRT
	M. O. Jarret	Expert, Biomechanical Engr.	RM	CC
	G. C. Hunt	Physical Therapy Research Coord.	RM	CC
	W. Schneiderwind	Chief, Physical Therapy Service	RM	CC
	N. L. Gerber	Chief, Rehabilitation Med. Dept.	RM	CC

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

Rehabilitation Medicine Department Computer System

This project involves the development of computer techniques in collaboration with the Department of Rehabilitation Medicine of the NIH Clinical Center. Techniques are being implemented to automatically acquire anatomical and physiological information from patients, perform required calculations on the data obtained, and display necessary results to the medical staff. The techniques include the measurement of body forces (hand and ground reaction forces), electromyograms (electrical activity of the muscles), and body kinematics (the position and angles of the limbs and joints in space and time). An Automated Biomechanics Laboratory System that provides these measurements has been purchased.

The computer part of the system will allow the medical staff to enter patient and staff data into a data base with computer generated forms displayed on a terminal screen, and to perform inquiries and generate reports using the accumulated data. In FY84, the purchased system was installed in a temporary location of the Clinical Center while plans for the final laboratory location were completed.

Background and Objectives: The Department of Rehabilitation Medicine provides physiatric evaluation and treatment, physical therapy, occupational therapy, and speech therapy for NIH Clinical Center patients referred by Institute physicians. In addition, it develops various indices to evaluate these services. This department supports the efforts of, and collaborates with, Institute physicians engaged in research relevant to physical rehabilitation medicine. It also initiates both clinical and basic research independent of the Institutes in the rehabilitation of mentally and physically handicapped individuals.

In support of these goals, CSL is developing a computer system. Initially, the department will use the system for the following three projects:

1. The Automated Biomechanics Laboratory: a laboratory that will be used to automatically measure the position of the limb segments in space, the patient ground reaction forces, and the electromyographic signals from the muscles in the limbs;
2. The Hand Dynamometer Instrument: a device that will be used to measure the magnitude and direction of the forces in the hand and to develop clinical tests to diagnose the mechanical and functional status of the hand, arm, and shoulder;
3. The Physical Therapy Quality Assurance System: a data base system that will be used to assess medical staff effectiveness in providing the types of patient care needed, to determine staff workload and scheduling, and to identify areas for clinical research for the Physical Therapy Service.

Progress in FY84: During the past year, the Automated Biomechanics Laboratory System purchased from Oxford Medilog, Inc., was installed in a temporary location of the Clincal Center. The instrumentation included five motion cameras with infrared light sources that are used to acquire the spatial coordinates of anatomical points on the patient's body with reflective markers, two force platforms that are used to measure patient ground reaction forces, and hard wired electromyogram acquisition hardware that is used to measure patient muscle activity.

This instrumentation is connected to a Digital Equipment Corporation VAX-11/750 computer system that performs the necessary data acquisition, calibration, processing, display, and storage functions.

The development of the Physical Therapy Quality Assurance Data Base System was initiated by the Department of Rehabilitation Medicine staff on this system using the VAX-11 DATATRIEVE Data Mangement Facility, the VAX-11 Common Data Dictionary, and the VAX-11 Forms Management System. The design of the permanent physical space for the laboratory was completed.

Also, during the past year, the collaboration with the Gait Analysis Laboratory, Department of Orthopedic Surgery, Children's Hospital Medical Center, and Harvard Medical School was continued. In the future, computer programs, patient data, and engineering and medical expertise will be exchanged with this group.

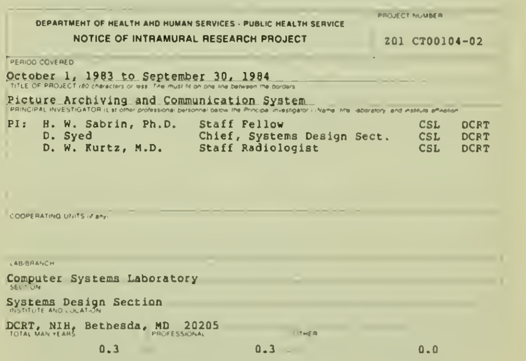
Significance to Biomedical Research: The computer system will be used to evaluate the effectiveness of drug therapy, orthotic and prosthetic devices, and medical interventions on patients who are amputees, or have arthritic, orthopedic, and neurological conditions. It will also be used as a teaching tool to help these patients learn to function with their disability in an efficient manner. Many medical centers in the United States, Great Britain, Europe, and Japan are presently establishing automated biomechanics and gait analysis laboratories. Therefore, any new developments made on this project will benefit users of these automated systems, as well as patient care and clinical research within the Department of Rehabilitation Medicine at NIH.

Proposed Course: During the coming year, the Automated Biomechanics Laboratory System will be placed in clinical operation. Initially, the mechanics of motion of amputees and the impact of prosthetic design on gait characteristics will be evaluated. Also, the effects shoe orthoses and hand splints may have for contiguous joints of the upper and lower extremities in arthritics will be studied.

Completion of the final laboratory location is scheduled for FY85, at which time the computer system and instrumentation will be moved from the temporary site. Many additions will be made to the system in the future including improvement of the EMG acquisition hardware; selection and integration of visual cameras and video recorders, including the electronics needed for synchronization with the motion cameras; implementation of energy expenditure calculation software; and the development of methods for accurately determining the velocity and acceleration of anatomical points from acquired motion data, including consideration of the required camera resolution and frame rate and digital differentiation techniques.

Publications:

Martino, R. L., and Gerber, L. H.: An Automated Biomechanics Laboratory Applied to Rehabilitation. *Proceedings of the Fifth Annual Conference of the IEEE Engineering in Medicine and Biology Society.* 1983, pp. 150-153.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00104-02

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Picture Archiving and Communication System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H. W. Sabrin, Ph.D.	Staff Fellow	CSL	DCRT
	D. Syed	Chief, Systems Design Sect.	CSL	DCRT
	D. W. Kurtz, M.D.	Staff Radiologist	CSL	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Picture Archiving and Communication System

This project encompasses the development of a picture archiving and communications system (PACS) to automate the storage and transmission of medical images at the Clinical Center. Although centered around the Diagnostic Radiology Department, the system is being designed with the long-term goal of serving other imaging-oriented departments, including Nuclear Medicine and Radiation Oncology.

The system will consist of state-of-the-art mass storage devices, which will be able to keep several week's worth of data available for immediate viewing, as well as the most advanced network communication, data management, and image display equipment. When in place, the system will allow the storage of images from several modalities in a central facility and will enable physicians to view those images from a variety of locations.

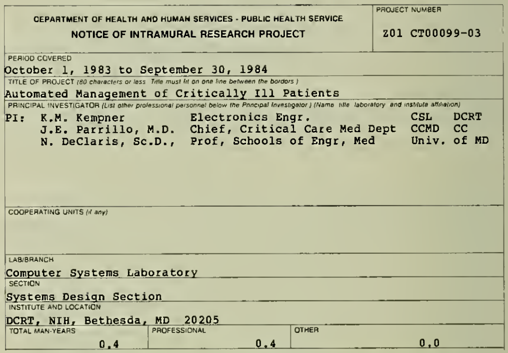
Background and Objectives: In addition to the traditional film x-ray, medical imaging today encompasses several new and complex modalities, among them Computed Tomography, Ultrasound, Digital Angiography, Scintillography, Emission Tomography, and others. Some of these modalities are digital in nature, while others produce images in video format. Storage of the images produced by these various devices is an arduous and space-consuming task, requiring separate film and tape libraries. A physician who wishes to view images generated on more than one of these devices must do so separately in the viewing areas for each modality, or must obtain hardcopy reproductions of the images.

The system proposed would enable the physician to view images of all modalities at a single location in a central viewing area. Additional viewing consoles could be placed in operating rooms, nursing stations, conference facilities and in clinical offices. Conversely, the same image can be viewed at several stations simultaneously. The system could allow quick access to images selected by individual patient, population group, illness, imaging modality, or other factors. A computer security system will prevent unauthorized individuals from gaining access to the image data base.

Progress in FY84: As a result of the feasibility study produced by CSL in FY83, the Clinical Center proposed substantial funding for a system in FY86.

Significance to Biomedical Research: An image management system like the one described above would greatly facilitate research by providing access to different classes of medical images. A physician wishing to compare images from different modalities, or conduct longitudinal or cross-population studies would be able to select and view all the images of interest in one session, while sitting at a single viewing station.

Proposed Course: When the Clinical Center has the funds available, we will proceed with the final specifications, procurement, and development of the system.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00099-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Automated Management of Critically Ill Patients

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: K.M. Kempner	Electronics Engr.	CSL	DCRT
J.E. Parrillo, M.D.	Chief, Critical Care Med Dept	CCMD	CC
N. DeClaris, Sc.D.,	Prof, Schools of Engr, Med	Univ. of MD	

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.4	0.4	0.0

Automated Management of Critically Ill Patients

This research project is concerned with a systems approach to the management of critically ill patients in a clinical setting. The ultimate goal is the utilization of computer-based instrumentation to aid in the differential diagnosis of disease states and the implementation of therapeutic modalities through automated technology.

A state variable approach is utilized in the mathematical modeling of pertinent pharmacokinetic and physiologic processes. Empirical clinical data and realtime monitored values are utilized in model validation. Several alternative methods for closed-loop automated medical interventions are being investigated.

Background and Objectives: Noninvasive diagnostic and therapeutic techniques generally involve the application of sophisticated electronic technology and mathematical modeling techniques to the detection of pathophysiologic states. Particularly interesting and important problems involve cardiovascular disorders that give rise to low output syndrome.

There is no singular cause for this syndrome, and therefore effective therapy requires the differential diagnosis of numerous contributory disturbances in cardiovascular homeostasis. Effective therapy principally involves the administration of one or more fluids and/or drugs in a critical care unit environment.

Methods Employed: In order to accomplish the goal of developing systems capable of assisting in the medical management of a critically ill patient on a closed-loop basis, it will be necessary to develop validated models. Calculated physiologic parameters will be compared to measured physiologic data as the patient's response to the selected therapy progresses.

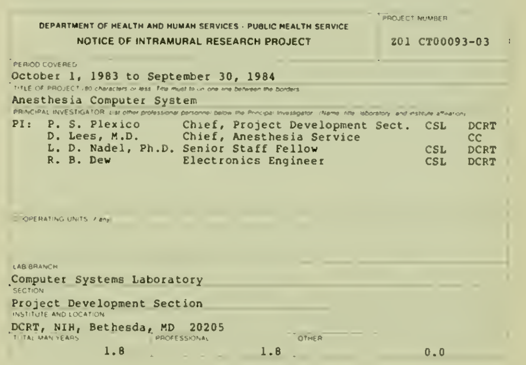
A mathematical formulation of the relevant subsystems was developed for a patient in a critical care unit setting. This includes the modeling of three principal subsystems: Pharmacokinetics, Drug/Receptor Interactions, and Cardiovascular Dynamics. Progam output includes recommendations for therapy as well as predicted pre- and post-intervention physiologic data values.

Progress in FY84: The package of FORTRAN programs, which models the drug administration protocol, and the three major subsystems accounting for drug action on cardiovascular function, have been completed. These programs, implemented on the IBM System 370 facility, simulate the intensive care unit environment and the patient's response to the theoretical chemotherapeutic interventions. Preliminary model studies indicate an instability in the cardiovascular dynamics model, due to inadequacies in the analytic expressions for the forcing functions representing myocardial contractility.

Significance to Biomedical Research: The use of automated systems in the implementation of therapeutic protocols within a critical care unit adds a new treatment modality and will have a major effect on protocol design. It will afford improvements in protocol design for patient care, clinical drug trials, and the study of the etiology and therapy of specific disease entities. In addition, the automation of therapeutic interventions, as proposed, will significantly expand the clinical and research data bases.

Proposed Course: Modifications will be incorporated into the cardiovascular dynamics model to provide a more appropriate representation for myocardial function. Existing critical care protocols will be investigated to identify those components in which automated therapeutic modalities can easily be accommodated within the framework of this research effort. An important aspect to be evaluated is the risk to the patient versus the realizable benefits.

Selected protocols will be implemented utilizing the closed-loop techniques developed in this project, with the objective of carrying out controlled clinical trials and quantitatively evaluating their effectiveness.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00093-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Anesthesia Computer System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	P. S. Plexico	Chief, Project Development Sect.	CSL	DCRT
	D. Lees, M.D.	Chief, Anesthesia Service		CC
	L. D. Nadel, Ph.D.	Senior Staff Fellow	CSL	DCRT
	R. B. Dew	Electronics Engineer	CSL	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.8	1.8	0.0

Anesthesia Computer System

This project involves evaluating improved instrumentation techniques and identifying and investigating ways that automation can benefit anesthesia. Project emphasis is on adjunctive monitoring and automated recordkeeping in the operating room.

Background and Objectives:

While computers and automation have been used in intensive care settings for some time, little previous work has been reported on their application in operating rooms. Three areas of potential benefit of an anesthesia computer have been identified:

1. Adjunctive monitoring, i.e., using the computer for monitoring and display of patient parameters. The main goals are a unified, easy to read display; limit detection and trend analysis of the parameters; and archiving of the measurements for later use in research or anesthesia mishap analysis.
2. Automated recordkeeping, in which the computer would not only record the results of monitoring, but

also make provisions for a record of drug administration, for free text notes by the anesthesiologist, and for producing a printed record suitable for inclusion in the patient's record.

3. Noninvasive determinations of additional parameters relevant to a patient's physiologic status.

An advantage of such a system is that it will allow the anesthesiologist to devote more time to the patient by simplifying the tasks of observing and recording measurements. An added potential advantage is an intelligent system of alarms to warn of a patient's deteriorating condition. Present alarm systems often are disarmed due to false triggering.

Progress in FY84: An overall design was developed for this data acquisition, analysis, display, and reporting system. Commercially available patient monitors will be used for front-end data acquisition. A microcomputer configuration based on a PDP-11/23 with the RSX-11-M operating system was selected, as were compatible components for data acquisition and display. Equipment delivery is expected by the end of FY84. In the meantime, software development has begun, using CSL's PDP-11/70 system.

To let anesthesiology determine the value of monitoring a patient's respired gas concentrations by mass spectrometry, a system using a DEC MINC 11/23, a graphics display, and a Perkin-Elmer MGA 1100A gas mass spectrometer was developed. Both realtime and trend plots of oxygen, carbon dioxide, nitrous oxide, and halogenated anesthetic gas concentrations are produced for the duration of a surgical procedure.

Most NIH surgical patients have their respiratory carbon dioxide levels monitored by Puritan-Bennett infrared analyzers. Concentration is indicated on a front panel analog meter. Anesthesiologists think the actual carbon dioxide waveform may provide a better indication of the patient's condition. To test the hypothesis, circuitry was designed to interface the infrared analyzer to an unused channel of the Vitatek 511 patient monitor. This interface adds a realtime carbon dioxide waveform display to the Vitatek's screen. Thus, the anesthesiologist may choose to monitor respired carbon dioxide either by infrared analysis or by mass spectrometry.

Proposed course: Software development will continue on the PDP-11/70 until the ordered hardware has arrived. The anesthesia system will then be integrated and software already developed will be adapted and transferred to the target system. Remaining software development and any necessary hardware design then will be carried out.

A preliminary system incorporating the existing O.R. monitoring protocol should be ready for testing during FY85. Pulmonary functions as well as any additional desired parameters and capabilities will then be added to the system, as will respiratory monitoring by mass spectrometry. Beyond that, plans include the development of a comprehensive computer-printed O.R. record, and algorithms for "intelligent" alarms. Improved methods of interaction between the anesthesiologist and the computer using technologies such as voice input/output, touch screen, handwriting recognition, and flat panel display also will be evaluated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00065-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Medical Information Technology Project

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. I. Allen	Medical Research Analyst	CSL	DCRT
	D. C. Songco	Electronics Engineer	CSL	DCRT
	C. S. Brown	Consulting Dermatologist		
	P. S. Plexico	Chief, Project Development Sect.	CSL	DCRT
	A. W. Pratt	Director		DCRT
	R. Moore	Computer Assistant	CSL	DCRT

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.5	1.25	0.25

Medical Information Technology Project

This project involves the application of microprocessor technology and improved man-machine interface methods to permit physicians and their associates to communicate more directly with computer record systems. A pilot study involving medical transactions entered directly by practicing physicians is in its third year. The goal is to develop better ways to automate the essential physician contribution to the health care record that is used in both research and patient care.

Background and Objectives: The use of computers in medical and hospital practice is increasing as the cost of systems is decreasing due to technological innovation. However, few physicians are comfortable with current machine interfaces. With this in mind, we are investigating devices and methods that provide a more capable, attractive interface while maintaining an acceptable level of flexibility and efficiency. The aim is to increase physician productivity in recording patient diagnoses and treatments, and to increase patient understanding of disease processes and management plans.

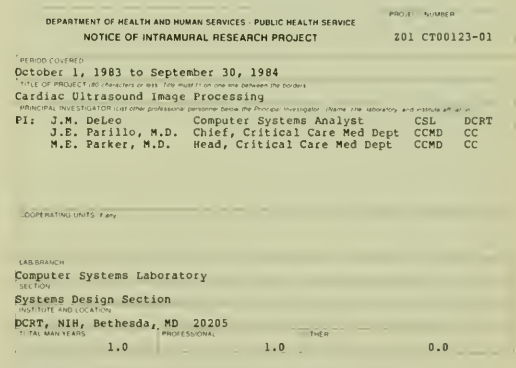
Progress in FY84: In collaboration with a practicing dermatologist and a gastroenterologist, we are field testing an ambulatory patient care transaction system. This system allows the physician to enter, store, retrieve, and disseminate patient data needed by various members of the health care team as well as by the patient. The immediate data processing focus includes machine generation of patient information and treatment schedules, pharmacy prescriptions, and medical and surgical procedure reports.

Disease-specific and problem-specific protocols are used to lead the user through a restricted tree-structured hierarchy of relevant diagnoses, treatments, drugs, tests, and procedures. Where appropriate, protocols are modified by such factors as patient age, sex, weight, disease stage, and therapeutic response specified by physician. When all workups and treatments are indicated, the computer produces hardcopy treatment plans for the patient, record summaries for the doctor, prescriptions for the pharmacist, and test requests for specified laboratories.

Much of the clinical software is table-driven to allow the physician to update the data bases. This approach also provides a convenient means of adapting the programs to other clinical care and research environments. Clinical data bases designed by collaborating physicians first are tested on a CSL microcomputer system. Finished programs, ready for use in patient care, are then transferred to a compatible microcomputer system situated in the physician's office.

Proposed Course: Selected physician-operated modules will be enhanced to support critical diagnostic and therapeutic functions in ambulatory care specialties. Programming logic to support isolated patient encounters also will be expanded to display key data from prior visits. The system design will be expanded to include a local area network capability to link various I/O terminals and medical file handling devices in both offices and clinics.

The conventional CRT and keyboard terminal employed now will be augmented with faster I/O devices that are tailored to this medical application. For example, we plan to use graphic input to facilitate the capture of anatomic disease descriptions and keyboard substitutes to speed menu item selection.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00123-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Cardiac Ultrasound Image Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.M. DeLeo	Computer Systems Analyst	CSL	DCRT
	J.E. Parillo, M.D.	Chief, Critical Care Med Dept	CCMD	CC
	M.E. Parker, M.D.	Head, Critical Care Med Dept	CCMD	CC

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

Cardiac Ultrasound Image Processing

This project is directed towards providing the NIH Clinical Center Medical Intensive Care Unit with the ability to assess cardiac left ventricular function via computer analysis of ultrasound images of the heart.

Background and Objectives: The objective of this project is to investigate the efficiency and practicality of assessing left ventricular function from ultrasound images in the clinical setting. Ultrasound technology has advanced so that fairly sharp images are computer accessible directly in realtime; ultrasound imaging is less invasive than currently popular cineangiography and nuclear imaging methods; and advances in image processing technology and technique have provided the necessary computer hardware and software capability.

Methods Employed: Ultrasound images captured on an HP77020A Ultrasound Imaging System are transmitted directly to an HP2100 Computer System. Image processing algorithms will be employed for image enhancement and contour extraction to estimate minimum and maximum left ventricular volumes for computing ejection fractions.

Progress in FY84: An investigation of earlier work has led to the development of design criteria for an interactive image processing methodology for estimating left ventricular ejection fraction. The hardware/software link between the ultrasound system and the remote computer exists. Software drivers and the utility programs have been written. A software package for collecting, processing, and displaying images and computing ejection fractions is under development.

Proposed Course: Future efforts will center on the evaluation of image processing and derived parameter algorithms in a clinical environment. These algorithms and techniques will be modified as necessary to improve their ability to estimate left ventricular ejection fraction and other computed parameters.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00124-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
PC System for Automatic Coronary Venous Flow Measurements

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: R.B. Dew Electronics Engineer CSL DCRT
M. Leon, M.D.

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.25	0.25	0.0

Personal Computer System for Automatic Coronary Venus Flow Measurement

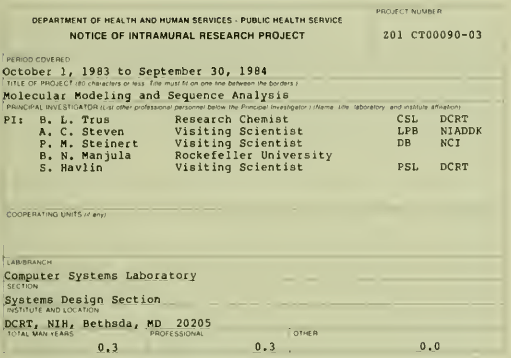
This project involves using a IBM Personal Computer to automate the acquisition and analysis of coronary venous blood flow measurements.

Background and Objectives: Cardiac catheterization procedures in the clinical setting often require immediate analysis of information concerning cardiovascular function. In determining coronary blood flow measurements, strip chart recording provides continuous monitoring of realtime analog waveform data. The investigator is handicapped, however, by the time needed to abstract flow information from the waveform plots and perform subsequent mathematical calculations. This project investigates how automated data acquisition and analysis may improve the speed and accuracy of coronary venous blood flow measurements.

Progress in FY84: The computer configuration selected was an IBM Personal Computer equipped with a Data Translation DT-2801-A I/O Board to sample analog voltage signals passed from a Baim Coronary Sinus Flow Analyzer. While awaiting system procurement, interface and software design and development was done on a CSL PC using simulated data, and later integrated into a PC bought by the Cardiology Branch.

The system was designed to continuously collect and process cardiac catheterization data from the flow analyzer and calculate regional coronary venous blood flow. Results from each flow calculation can be displayed on the PC's CRT screen and stored on a disk file. Hardcopy recording of case results is provided by an Epson FX-80 dot matrix printer, which both can plot graphical information and print tabulated alphanumeric records.

Proposed Course: A dedicated work station will be set up in the Cardiac Catheterization Lab to test system functionality and to evaluate its contribution to clinical investigation.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CT00090-03

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Modeling and Sequence Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. L. Trus	Research Chemist	CSL	DCRT
	A. C. Steven	Visiting Scientist	LPB	NIADDK
	P. M. Steinert	Visiting Scientist	DB	NCI
	B. N. Manjula	Rockefeller University		
	S. Havlin	Visiting Scientist	PSL	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH

Computer Systems Laboratory

SECTION

Systems Design Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethsda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Molecular Modeling and Sequence Analysis

The sequence of some regular proteins, together with other structural information such as data from x-ray diffraction, fiber diffraction, electron microscopy, and spectroscopic analysis can be used to evaluate models of protein structure. Four current studies involve keratin and other intermediate filaments (with NIADDK, NCI), actin (with NIADDK), streptococcal M5 protein (with Rockefeller University), and models of branched polymers (with PSL, DCRT).

Background and Objectives: It is currently possible to convincingly model and predict the structure of regular (helical) proteins. With the current knowledge of the structure of the collagen helix, synthetic protein analogues of collagen, tropomyosin, and other regular proteins, one can extend this technology to new proteins as their sequence is determined experimentally.

As the complete sequence of keratin, other intermediate filaments, and other helical proteins becomes available, an anaylsis of the sequence can proceed by studying periodicities in the sequence, and by computer prediction of the conformational properties of the specific amino acids in local regions of the chain. These predictions can be used to generalize structures where related sequences are available, and to draw conclusions as to similarities and differences.

Significance to Biomedical Research: Many proteins do not form three-dimensional crystalline solids whose structure can be analyzed by classical x-ray diffraction. However, if these proteins are regular, comparison and analogy with related proteins can be used to model the unknown structures in order to understand the structure and functioning of the proteins. In addition, one can use computer models to analyze possible protein structures based on criterion other than regular periodicities.

Progress in FY84: Analysis of the first complete sequence of a type II keratin has been completed and submitted for publication. Additionally, these results can be compared with the analysis of the first complete type I keratin we published last year. The distribution of periodicities in a biologically active Streptococcal M5 protein have been analyzed with their corresponding relation to structure. This work also has been submitted for publication. Computer models have been used to study the growth of branched polymers, and these results have been submitted for publication. A detailed comparison of the diffraction patterns from stained and unstained helices has been completed using computer simulations with defined model structures. These results were presented at the Eighth European Congress on Electron Microscopy, and have been submitted for publication.

Methods Employed: Standard Fourier methods have been used to analyze the sequences and to cross-correlate sequences. These sequence regularities are usually correlated with structural features, such as the collagen triple helix, the alpha helix, or the tropomyosin double stranded alpha helix. Additional software has been developed at NIH to illustrate correlations and create maps of the linear sequences studied. We have developed other methods of model building to construct models of actin, actin with S1 subunits, microtubules, and simple branched polymers.

Proposed Course: As new sequences of regular (helical) proteins become available, it is relatively easy to model these sequences and describe their structures both graphically and quantitatively.

Publications:

Steinert, P. M., Parry, D. A. D., Rocoosin, E. L., Idler, W. W., Steven, A. C., Trus, B. L., and Roop, D. R.: The Complete cDNA and Deduced Amino Acid Sequence of a Type II Mouse Epidermal Keratin of 60,000 Molecular Weight: Analysis of Sequence Differences Between Type I and Type II Keratins. *Proc. Natl. Acad. Sci. USA* (in press).

Trus, B. L., and Steven, A. C.: Comparison of Diffraction Patterns from Stained and Unstained Helices: Simulations with Defined Model Structures. In Csanady, A., Rohlich, P., and Szabo, D. (Eds.): *Proceedings of the Eighth European Congress on Electron Microscopy*. Bud1984, pp. 1355-1356.

Trus, B.L., and Steven, A.C.: Diffraction Patterns from Stained and Unstained Helices: Consistency or Contradiction. *Ultramicroscopy* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00080-04

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Computer Analysis of Gel Electrophoresis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B.L. Trus	Research Chemist	CSL	DCRT
	N. Grossman	Staff Fellow	LBP	NIADDK
	T. Pun	Staff Fellow	BEIB	DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.1	0.1	0.0

Computer Analysis of Gel Electrophoresis

This project was designed to allow NIH scientists to easily and accurately quantitate one- and two-dimensional gels. New software is being developed to utilize the features of the new image processing facility and more easily and quickly to analyze gels, autoradiographs, and hybridization experiments.

Background and Objectives: The primary objective of this project has been to develop experimental techniques and computer software to easily and automatically quantitate one- and two-dimensional gels. Initially only Coomassie blue stained gels were analyzed, but currently autoradiographs are equally amenable to processing.

Significance to Biomedical Research: Use of gel electrophoresis and autoradiographs is commonplace in chemical, biochemical, and biomedical research. However, the quantitation of these gels is difficult. We have developed systems that accurately and easily provide this quantitation to the scientist.

Progress in FY84: This project has produced useful results to a number of scientists at NIH. New methodology currently is being developed in collaboration with the Biomedical Engineering and Instrumentation Branch (BEIB), DRS, to automatically and quickly analyze 1-D gels. This new proceedure automatically locates lanes, subtracts background, and integrates the total content across each lane. The results are depicted graphically, and a printout is produced that includes a summary and simple plot.

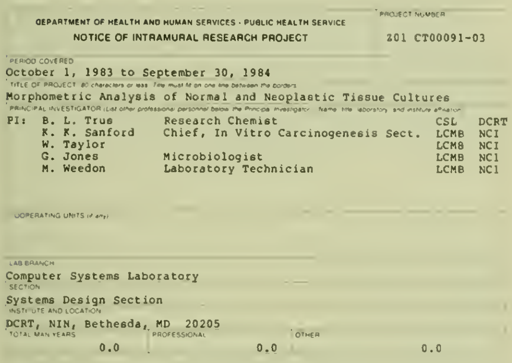
Methods Employed: Wet gels are rephotographed onto Ektapan 4162 black and white film. The black and white negative (4162 or an autoradiograph) is scanned on the Perkin-Elmer microdensitometer and stored on disk for later processing. Software to process these images was developed primarily at NIH.

Proposed Course: New software is being developed that will provide better background correction. In addition, present methods will be adapted to include hybridization experiments. Additional options are being added to the software to provide additional flexibility to the research scientist.

Publications and Presentations:

Nikodem, V.M., Huang, D.R., Trus, B.L., and Rall, J.E.: The Effects of Thyroid Hormone on In Vitro Phosphorylation, Acetylation, and ADP Ribosylation of Rat Liver Nuclear Proteins. *Horm. Metab. Res.* 15: 550-554, 1983.

Pun, T., Trus, B., Grossman, N., Leive, L., and Eden, M.: Automated Computer Analysis of 1D Electrophoresis Gels by Image Processing. Symposium on Biomedical Applications of Computers, National Institutes of Health, August 6-10, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00091-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Morphometric Analysis of Normal and Neoplastic Tissue Cultures

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. L. Trus	Research Chemist	CSL	DCRT
	K. K. Sanford	Chief, In Vitro Carcinogenesis Sect.	LCMB	NCI
	W. Taylor		LCMB	NCI
	G. Jones	Microbiologist	LCMB	NCI
	M. Weedon	Laboratory Technician	LCMB	NCI

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory
SECTION
Systems Design Section
INSTITUTE AND LOCATION
DCRT, NIN, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.0	0.0	0.0

Morphometric Analysis of Normal and Neoplastic Tissue Cultures

This pilot project was designed to study the morphometric differences between normal and tumorigenic fibroblastic cell lines. Initially, human, rat, and mouse cell lines were selected for analysis. The cells were photographed from living cultures without staining or fixing. The types of criteria being used by the computer to aid in differentiating between normal and tumorigenic cells include nucleus and nucleolus size and shape, and chromatin texture and clumping.

Background and Objectives: This project uses standard techniques of image processing, as applied to these low contrast unstained specimens, as well as techniques developed at NIH. We have demonstrated that it is possible and practical to differentiate between normal and tumorigenic cells in a nondestructive manner, using many of the same criteria used by pathologists in differentiating stained and fixed sections.

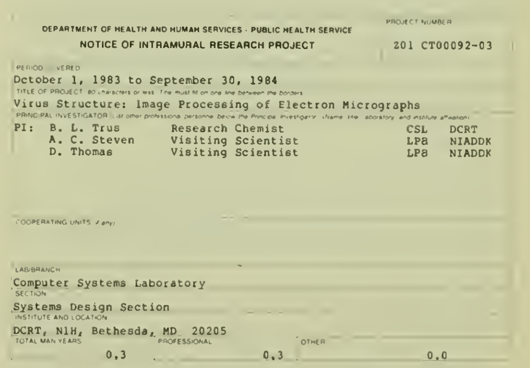
Significance to Biomedical Research: We demonstrated that this nondestructive method can be used with confidence to determine if a culture is normal. This method would be important for studies of carcinogenesis in cultures.

Progress in FY84: DCRT participation in this project was terminated this year.

Methods Employed: Cell cultures were photographed through a light microscope onto 35mm black and white film. The film was digitized by a Perkin-Elmer 1010G microdensitometer with a 50 square micron aperture. Images were viewed on a video frame buffer and processed interactively. Results are stored in log files for each sample, and files are pooled for each type of culture, yielding better statistics. The mouse and rat cultures underwent spontaneous neoplastic transformation, while the human fibroblast line was exposed to chemical carcinogens to generate the tumorigenic line.

Publications:

Taylor, W. G., Camalier, R. F., Trus, B. L., and Sanford, K. K.: Differences in Area and Distribution of Focal Adhesion Sites Accompany Cell Shape Changes after Neoplastic Transformation. *J. Cell Biol.* 97: 451a, 1983.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00092-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Virus Structure: Image Processing of Electron Micrographs

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. L. Trus	Research Chemist	CSL	DCRT
	A. C. Steven	Visiting Scientist	LPB	NIADDK
	D. Thomas	Visiting Scientist	LPB	NIADDK

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory
SECTION
Systems Design Section
INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Virus Structure As Determined by Image Processing of Electron Micrographs

A new virus structure, that of Vesicular Stomatitis Virus (VSV), currently is being studied. The structure was determined by image processing of electron micrographs together with Scanning Transmission Electron Microscopy (STEM) data. In addition, a new method has been developed to perform radial reconstructions on STEM projections of cylindrically symmetrical structures.

Background and Objectives: By studying the structure of selected viruses, we increase our understanding of similar or related viruses. It is our primary objective to add to the pool of information, and to be able to use this information to increase our understanding about how virus structure relates to function and activity.

Progress in FY84: Significant progress has been made in understanding the structure of the VSV virus. The radial reconstruction method, recently accepted for publication, provides scientists with a simple real space algorithm for analysis of projection data to provide radial reconstructions. The method was applied to Tobacco Mosaic Virus (TMV) as a test case, for the structure of TMV is relatively well known.

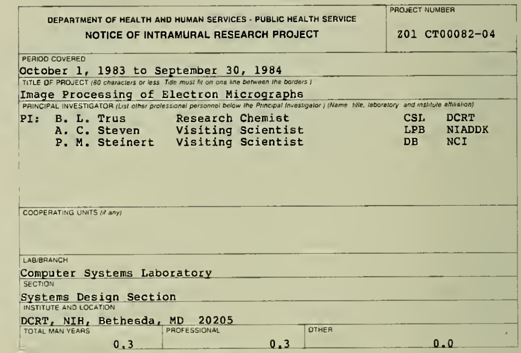
Methods Employed: The micrographs were taken with a Philips EM400T microscope and the Brookhaven STEM. Some micrographs were preselected by optical diffraction. Negatives were digitized on a Perkin-Elmer 1010G microdensitometer and analyzed by means of the PIC computer system. Results were photowritten on the Perkin-Elmer microdensitometer. Images were processed using software developed primarily at NIH.

Proposed Course: We anticipate evaluating other viruses for suitability for examination with these methods, and continuing with this ongoing project to determine the structure of various classes of viruses.

Publications and Presentations:

Steven, A. C., Hainfeld, J. F., Trus, B. L., Steinert, P. M., and Wall, J. S.: Radial Distributions of Density Within Macromolecular Complexes Determined from Dark-Field Electron Micrographs. *Proc. Natl. Acad. Sci. USA* (in press).

Thomas, D., Newcomb, W. W., Brown, J. C., Wall, J. S., Hainfeld, J. F., Trus, B. L., and Steven, A. C.: Mass Determination and Molecular Composition of Vesicular Stomatitis Virus: A Stem Analysis. Annual Meeting of the French Society of Electron Microscopy, Lyon, France, May 12-24, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00082-04

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Image Processing of Electron Micrographs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. L. Trus	Research Chemist	CSL	DCRT
	A. C. Steven	Visiting Scientist	LPB	NIADDK
	P. M. Steinert	Visiting Scientist	DB	NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Image Processing of Electron Micrographs

This project was designed to facilitate structure determination from electron microscopy by providing suitable software, hardware, and scientific expertise to allow other scientists, primarily at NIH, to use image processing and computer reconstruction to determine or understand a specimen's structure.

Background and Objectives: The objective of this project is to develop a general-purpose software package for the analysis of electron micrographs. In addition, the computer analysis requires optimal utilization of the available hardware and the availability of a research scientist capable of providing logistical support. Techniques and software developed in this project have been used at other laboratories at NIH and elsewhere.

Significance to Biomedical Research: Computer analysis of electron micrographs is still a relatively recent addition to the tools available to scientists for structural analysis. Few laboratories have the combined software and hardware capability to perform the image processing and image reconstruction available at NIH. These techniques are especially powerful when applied to two-dimensional crystalline structures. In addition, we can correlate and align similar particles that are not crystalline, and correct for a number of artifacts and experimental problems.

Progress in FY84: Studies continued from FY83 include analysis of keratin and other intermediate filaments. This project has generated some additional software, but primarily has focused on utilization of existing programs and the PIC system. It is feasible for an NIH scientist to bring in a problem and obtain preliminary results in a relatively short period of time; then, a decision is made to expand the preliminary study into a project or to use the results obtained.

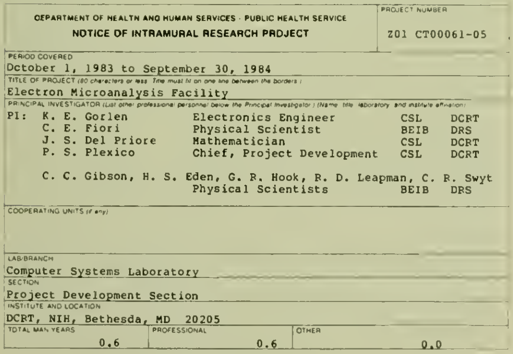
Proposed Course: This project will continue software development as needed. In addition, as new biological structures become available for analysis, these will be examined.

Publications and Presentations:

Steven, A. C., Hainfeld, J. F., Trus, B. L., Wall, J. S., and Steinert, P. M.: Epidermal Keratin Filaments Assembled in Vitro Have Masses-per-Unit-Length That Scale According to Average Subunit Mass: Structural Basis for Homologous Packing of Subunits in Intermediate Filaments. *J. Cell Biol.* 97: 1939-1944, 1983.

Steven, A. C., Hainfeld, J. F., Trus, B. L., Wall, J. S., and Steinert, P. M.: The Distribution of Mass in Heteropolymer Intermediate Filaments Assembled in Vitro. *J. of Biol. Chem.* 258: 8323-8329, 1983.

Steven, A. C., Trus, B. L., Hainfeld, J. F., Wall, J. S., and Steinert, P. M.: Conformity and Diversity in the Structures of Intermediate Filaments. International Conference on Intermediate Filaments, NY Academy of Sciences, May 21-23, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00061-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Electron Microanalysis Facility

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	K. E. Gorlen	Electronics Engineer	CSL	DCRT
	C. E. Fiori	Physical Scientist	BEIB	DRS
	J. S. Del Priore	Mathematician	CSL	DCRT
	P. S. Plexico	Chief, Project Development	CSL	DCRT
	C. C. Gibson, H. S. Eden, G. R. Hook, R. D. Leapman, C. R. Swyt	Physical Scientists	BEIB	DRS

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.6	0.6	0.0

Electron Microanalysis Facility

CSL is collaborating with BEIB, DRS, in developing an automated electron microanalysis facility consisting of two electron microscopes interfaced to a computer system. The facility is being used for research into the elemental composition of biological specimens, and for the development of new techniques in electron microscopy. CSL designed and implemented the computer system, which acquires and displays the spectra and images produced by Electron Energy Loss Spectrometry, Energy-Dispersive x-ray Spectrometry, and Wavelength Dispersive x-ray Spectrometry.

Background and Objectives: The Computer Systems Laboratory designed and implemented a computer system as part of the BEIB Electron Beam Imaging and Microspectroscopy Facility.

One of the electron microscopes is an Hitachi H-700H 200 keV Scanning Transmission Electron Microscope (STEM) equipped with:

- a lithium-drifted silicon--Si(Li)--detector connected to a Kevex 7000 Analytical Spectrometer for performing Energy-Dispersive x-ray Spectrometry (EDS)
- an electron spectrometer for performing Electron Energy Loss Spectrometry (EELS)
- detectors for bright and dark field electron current signals.

The other electron microscope is a Cameca 50 keV Electron Microprobe equipped with:

- a Si(Li) detector for performing EDS
- three Wavelength Dispersive x-ray (WDS) Spectrometers
- detectors for bright and dark field electron current signals.

The PDP-11/60 computer system interfaced to both microscopes performs the following functions:

- controls electron beam position, stage position, and the various detectors
- acquires spectral and image data from all detectors
- processes and displays the spectral and image data.

Progress in FY84: The STEM is being used in three neurological investigations: Potassium, sulfur, and phosphorus x-ray images are being related to morphology in nerve terminals (synaptosomes); EEL images of nitrogen, sulfur, and phosphorus in chromaffin cells are being used to study the process of exocytosis; and the distribution of potassium and calcium in cryosections of the cerebellum is being studied to determine the effects of trauma.

The Cameca Microprobe continues to be used to image aluminum and calcium in neurofibrillary tangles in the brains of victims of Amyotrophic Lateral Sclerosis. In a new application, it is being used to image Cis-platinum in order to characterize the uptake of this element by various tissue types for purposes of cancer treatment.

CSL's efforts this past fiscal year have been devoted to enhancing the image display and data acquisition software, writing a paper describing the system for publication in *Review of Scientific Instruments*, and converting Pascal programs to the latest version of the compiler so they can be more easily maintained.

A significant improvement made to the data acquisition software allows "r-imaging" to be performed, which under certain circumstances can substantially reduce the noise in elemental images. After acquiring an image, the user examines the "r-image" to see if it contains information or is just noise. If it is just noise, an enhancement procedure, which assumes a constant value of r equal to the mean value of the "r-image," can be applied to improve the elemental image. Furthermore, the development of this technique has demonstrated the unreliability of the type of EEL imaging previously done with the STEM, which in effect performs the "enhancement" whether or not it is valid to do so, thereby potentially introducing artifacts in the EEL image.

Proposed Course: Although we hope to install a better EEL spectrometer (equipped with a usable dark-field detector) on the STEM next year, the system is as large as the current computer equipment reasonably can support and no other development is planned.

Publications and Presentations:

Fiori, C., Swyt, C., and Gorlen, K.: Continuum Correction of X-ray Images in Scanning Electron Column Instruments. In Goldstein, J.I., and Romig A. (Eds.): *Microbeam Analysis* (in press).

Gorlen, K.: The Computerization of an Analytical Electron Microscope. The Joint Meeting of Electron Microscopy Society of America and Microbeam Analysis Society. Phoenix, Arizona, August 1983.

Gorlen, K., Barden, L., Del Priore, J., Fiori, C., Gibson, C., and Leapman, R.: A Computerized Analytical Electron Microscopy for Elemental Imaging. *Rev. Sci. Instrum.* 55: 912-921, 1984.

Gorlen, K., Barden, L., Del Priore, J., Kochar, A., Fiori, C., Gibson, C., and Leapman, R.: A Data Acquisition System for an Analytical Electron Microscope. *Proc. of the Digital Equipment Users Society USA.* Fall DECUS, 1982, pp. 181-187.

Leapman, R., Fiori, C., Gorlen, K., Gibson, C., and Swyt, D.: Combined Elemental and STEM Imaging under Computer Control. *J. Ultramicrosc.* 12: 281-292, 1984.

Leapman, R., Fiori, C., Gorlen, K., Gibson, C., and Swyt, D.: Combined Elemental and Structural Imaging in a Computer Controlled Analytical Electron Microscope. *Proc. of the EMSA.* 1983, pp. 10-13.

Leapman, R., Gorlen, K., and Swyt, C.: Background Subtraction in STEM Energy Loss Mapping. In Bailey, G.W. (Ed.): *Proc. of the 42nd EMSA Meeting* (in press).

Leapman, R., Gorlen, K., and Swyt, C.: Digital Processing of Electron Energy Loss Spectra and Images. In Johnson, D. (Ed.): *Proc. of SEM 84* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00058-05

PERIOD COVERED
October 1, 1982 to September 30, 1983

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Californium-252 Plasma Desorption Mass Spectrometer Data System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R. L. Tate, Ph.D.	Computer Specialist	CSL	DCRT
	H. M. Fales, Ph.D.	Chief	LC	NHLBI
	L. Pannell, Ph.D.	Guest Worker	LC	NHLBI

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.4	0.4	0.0

Californium-252 Plasma Desorption Mass Spectrometer Data System

The Californium-252 plasma desorption mass spectrometer puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations. The spectrometer, modeled after one in use at Texas A & M University and its associated data system, has been functional for more than a year.

The Californium-252 time-of-flight (TOF) mass spectrometer employs nuclear fission fragments to ionize samples that frequently have proven intractable to other methods of analysis. This instrument now provides NIH the capabilities of mass analysis for compounds that have proven difficult or impossible to analyze by other mass spectrometric means. It also extends the range of mass analysis to compounds with molecular weights in excess of 5000. Classes of compounds recently analyzed include peptides, antibiotics, steroids, and dyes.

Background and Objectives: In this instrument, fission fragments generated by the radioactive decay of a thin film of 252-Cf impact on a thin layer of sample deposited on a conductive plastic film, producing a localized plasma. The sample molecules produced within this plasma are extracted by an electric field and briefly accelerated down an evacuated tube toward a microchannel plate ion detector. The elapsed times between the ionization event and the arrival of the ions produced are measured with an ultraprecise clock capable of measuring time intervals of hundreds of milliseconds with a resolution of 800 picoseconds. The elapsed time measurements are then sent to a computer where they are sorted, tallied, converted to mass units, and displayed.

The extended range of the timing clock coupled with the unique characteristics of the ionization process make this mass spectrometer ideally suited to the investigation of the high molecular weight compounds typical of biological materials. The data system was specified to be compatible with interface hardware and software available from Dr. Macfarlane.

The need for realtime sorting of a large volume of input data puts unusual and stringent demands on the data system that controls the spectrometer and acquires and processes its data output. Realtime performance and the ability to access very large data arrays in main memory are key considerations.

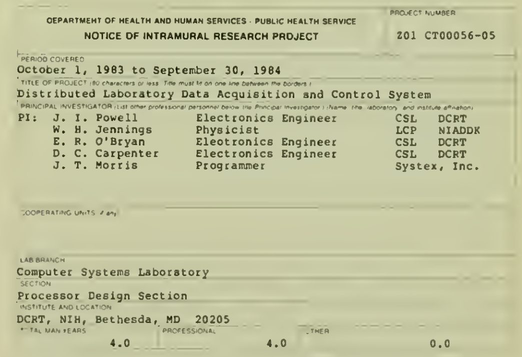
Progress in FY84: The process of software verification and reorganization is in its final stages. Extensive changes also were made to the structure of the COMMON program storage area to facilitate inclusion of sample and analysis parameters in the data files. Studies were begun on the nature of the ionization process, utilizing our capability to record each ionization event for further study. Computer system memory was expanded to 1024K bytes with the addition of an additional 256K bytes of memory. The addition of another selector channel dedicated to the spectrometer interface has resolved a number of subtle problems. Modifications were made to the mass spectrometer ion source to enhance resolution, permit both negative and positive ion spectroscopy, and improve its safety and reliability. Electronic monitors also were installed, to prevent catastrophic system failure in the event of vacuum and/or power loss.

Proposed Course: The major software additions anticipated are more programs for analyzing individual ionization events. Hardware improvements under consideration include replacement of the time-of-flight digitizer with one having a shorter dead time and further improvements in the ion source.

Publications and Presentations:

Pannell, L.K., Fales, H.M., Scovill, J.F., Klayman, D.L., West, D.X., and Tate, R.L.: Californium Plasma Desorption Mass Spectrometry of Some Metal-Ligand Complexes. ASMS 32nd Annual Conference, San Antonio, Texas, May 27-June 1, 1984.

Pannell, L.K., Fales, H.M., Sokoloski, L.C., and Tate, R.L.: Californium Plasma Desorption Mass Spectrometry of Cationic, Anionic, and Neutral Dyes. ASMS 32nd Annual Conference, San Antonio, Texas, May 27-June 1, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
201 CT00056-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Distributed Laboratory Data Acquisition and Control System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. I. Powell	Electronics Engineer	CSL	DCRT
	W. H. Jennings	Physicist	LCP	NIADDK
	E. R. O'Bryan	Eleotronics Engineer	CSL	DCRT
	D. C. Carpenter	Electronics Engineer	CSL	DCRT
	J. T. Morris	Programmer	Systex, Inc.	

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.0	4.0	0.0

Distributed Laboratory Data Acquisition and Control System (DLDACS)

An integrated laboratory data acquisition and processing system has been developed for LCP and LMB, NIADDK, in Building 2, NIH. The system is configured with satellites coupled through a local network to a host processor. Each satellite is a dedicated microcomputer system performing data acquisition from, and control over, an instrument/ experiment. Although acquired data files may be stored locally, they are normally tranferred via the network to a host storage medium. The local network allows the host storage medium to appear as a 'virtual' storage device to the satellites.

Background and Objectives: A system of microcomputers capable of independently controlling and acquiring data from an instrument/experiment was proposed in December, 1976 to replace the old LDACS designed by CSL in 1968 using a single computer to serve all instruments. Satellite configuration includes a Digital Equipment Corporation (DEC) LSI-11 microcomputer, 28K of memory, low density random access storage, graphics terminal, and all the necessary I/O hardware to interface the instrument/ experiment.

Software developed by CSL for each satellite, running under DEC's RT-11 operating system, provides the user with a turnkey system.

Instruments connected to the network include: spectrophotometers--the Cary 118, 210, and 219; two Perkin-Elmer 580B's; and a microspectrophotometer (designed by NIADDK)--and spectropolarimeters--Jasco J500A; a Varian Electron spin resonance spectrometer; I.S. Co. Model 1440 liquid chromatograph; a SPEX spectrometer (utilizing EG&G model 1420 intensified silicon photodiode array detector and model 1218 detector controller)--and a retinal stimulus reponse apparatus.

The local network includes a software module, installed at each satellite as a handler under the RT-11 operating system. Each satellite is connected via a hardwired serial link to a front-end concentrator. The concentrator performs a file store and forward function. Received files are placed in a first-in-first-out queue. Files are transferred from the queue to the host via a parallel DMA link. The communications task running on the host maps the files to the appropriate directory area based on the identity of the satellite that originated the transfer and the extension of the file being transferred.

The host processor--a DEC PDP-11/70--is configured with: 640K words of memory, a high-speed printer/ plotter, an X-Y plotter, a 9 track magnetic tape drive, dual RX02 floppy disk drives, RL02 disk drive, two large capacity RA-81 Winchester disk drives, an RP04 disk drive, a 4800-baud link to a DECSystem-10, and 32 serial I/O ports. DEC's multiuser, multitasking operating system--RSX-11M--is used to service the processing needs of the users.

Processing software provided at the host allows LDACS data files to be: added, subtracted, averaged, smoothed, baseline corrected, integrated, differentiated, multiplied by a constant, and added to a constant. The results may be displayed graphically on a Tektronix compatible terminal, typed on a terminal, printed on a line printer, plotted on an X-Y plotter or transmitted to the NIH DECSystem-10 system for additional processing.

Progress in FY84: The Cary 118 LDACS interface was replaced and new software provided. In order to accommodate melting run analysis of DNA structures, which melt at higher temperatures, the bath temperature controller interfaces were modified to allow the computer to set temperatures greater than 100 degrees Celsius. CSV-11A clock/timer boards were incorporated into the LDACS on the Stimulus Response experiment and on the Cary 118, 210, and 219. Software to perform kinetics, melting runs and multiscan averaging was developed for the Cary 210 and ported to the Cary 219 system. Software for multiscan averaging and melting runs was provided for the two PE 580B instruments.

Planning and design were initiated for the integration of a Raman spectroscopic instrument into the LDACS system. In response to a researcher's request for more flexibility in experimental control, an interactive data acquisition software package (DAOS) was purchased for use on the Stimulous Response LDACS.

A new version of the concentrator communications software was installed. This version added support for eight additional (total of sixteen) serial DMA I/O ports, while enhancing the status display and moving it to a serial DMA port. The status display port also is used for initialization testing. The memory pool allocation/deallocation routines were enhanced and the buffer size used to transfer files to the 11/70 was increased.

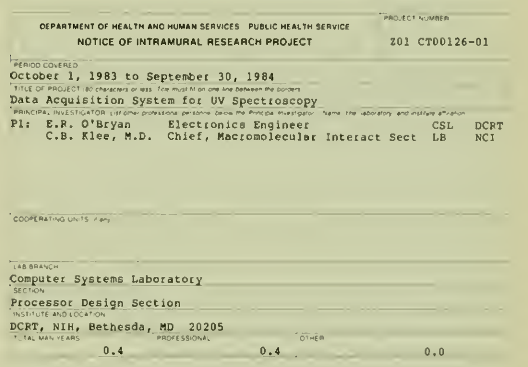
It was decided to rewrite APR, a program which was the combination of many processing programs. Many user-suggested enhancements were added, including: control-C abort of commands, nesting of indirect command files, optional user-written replacement command tables, enhanced graphics and plotting capabilities, header logging of commands that modify data, an 'IF ...THEN ... ELSE ...' command, and much more. This version of APR will be documented thoroughly.

The RA81 disk drives were installed in April and are now the system units. Sixteen additional serial I/O ports (EMULEX DH equivilent) and an RL02 disk drive have been incorporated into the system. RSX-11M-PLUS was purchased and delivered in February. We do not plan to convert to PLUS until it is installed on the CSL 11/70 development system.

Proposed Course: It is anticipated that some level of long-term support will continue. The retrofitting of LDACS units with up-to-date software and system documentation will be completed. New satellites or instruments may be added to the system, and existing LDACS aquisition programs may be modified to enhance data acquisition or to incorporate new instruments/experiments. Occasionally special purpose programs to process a set of experimental data will be required.

Publications:

O'Bryan, E. R.: Counter/Timer Peripheral for the DEC Q-Bus. *Proceedings of the Digital Equipment Computer Users Society*. Fall DECUS, pp. 217-221, 1983.



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00126-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Data Acquisition System for UV Spectroscopy

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E.R. O'Bryan	Electronics Engineer	CSL	DCRT
	C.B. Klee, M.D.	Chief, Macromolecular Interact Sect	LB	NCI

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Processor Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.4	0.4	0.0

Data Acquisition System for UV Spectroscopy

A data acquisition system was developed to collect data from a spectrophotometer, to transfer this data to the DCRT computer facility, and to facilitate analysis of the data by emulating a graphics terminal. The system is based on a Digital Equipment Corporation MICRO/PDP-11 microcomputer that is interfaced to a Cary Model 118 Ultraviolet Spectrophotometer.

This computer controls the spectrophotometer's monochrometer through a custom interface. Absorbance data is acquired from the instrument and stored locally. At a convienient time the stored data is transferred to the DCRT facility where analysis is performed by using the MLAB program. This system further assists the user by emulating a graphics terminal that is compatible with MLAB.

Background and Objectives: Development of a data acquisition system was requested by Dr. Klee in order to improve the collection and processing of data from a Cary Model 118 Ultraviolet Spectrophotometer. The System requirements were: accurate control of the spectrophotometer's monochrometer with concurrent acquisition of absorbance data; the ability to average absorbance data over multiple scans; local storage of the acquired data; data analysis using the MLAB program running on the DCRT PDP-10 Computer

Facility; and control of MLAB from the acquisition system terminal.

System development began in January, 1984, and was complete in March, 1984. The system uses a Digital Equipment Corporation MICRO/PDP-11 microcomputer. This computer controls the spectrophotometer's monochrometer through an interface designed and built at NIH. Absorbance data is acquired from the instrument and can be averaged over multiple scans. Data is stored locally, and at a convenient time, is transferred to the DCRT PDP-10 computer facility via a 1200-baud modem over a standard telephone line.

Analysis is performed with the data acquisition system communicating with the PDP-10 and emulating a Tektronix Model 4010 graphics terminal.

Progress in FY84: In addition to meeting our original objectives, several other functions were provided: communication with the DCRT IBM facility; communication with the National Library of Medicine's MEDLINE system; and plotting with a Hewlett-Packard HP2740A two-pen plotter.

Proposed Course: Development and installation of this system is complete, but CSL will continue to provide support in the form of minor additions and improvements, system maintenance, and user training.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00064-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Image Processing Facility

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Syed	Chief, Systems Design Sect.	CSL	DCRT
	W. L. Risso	Electronics Engineer	CSL	DCRT
	A. J. Pashayan	Computer Specialist	CSL	DCRT
	B. Trus	Research Chemist	CSL	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

Image Processing Facility

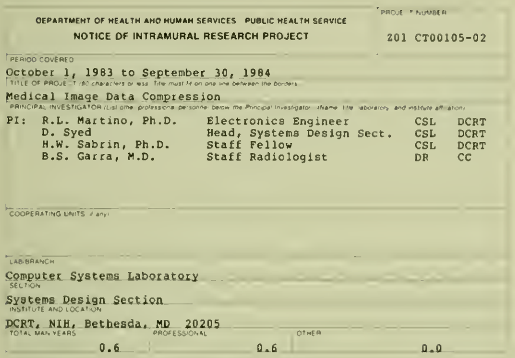
This project provides a utility to display and analyze digital images. The system consists of a powerful 32-bit computer with a mixture of medium-resolution and high-resolution displays and a smaller 16-bit processor to handle image acquisition. A high-resolution microdensitometer allows precision digitization of x-rays, micrographs, and other images. Hardcopy is provided by a camera system.

Background and Objectives: CSL undertook this project to alleviate a critically overcrowded DCRT graphics computer. As image processing applications at NIH increased, the limited resources of that graphics system became saturated. During FY80, CSL, in collaboration with present and potential users, designed a new general purpose computer facility for the acquisition, display, and analysis of images such as electron micrographs, CAT scans, and radiographs.

Progress in FY84: Two additional display stations were added this year, and the microdensitometer was put online under microprocessor control. A number of changes made to both systems and applications software improved speed and resource demands.

Significance to Biomedical Research: Study of images obtained in the biomedical laboratory is proving more fruitful as technology is able to supply the proper tools at a reasonable cost. Biomedical scientists are employing image analysis for a wide variety of research goals, and the use of such techniques is expected to grow very rapidly in the near future.

Proposed Course: Formal development of this system is now complete. Future work will be reported under the individual research topics studied with the system.



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
201 CT00105-02

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Medical Image Data Compression

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.L. Martino, Ph.D.	Electronics Engineer	CSL	DCRT
	D. Syed	Head, Systems Design Sect.	CSL	DCRT
	H.W. Sabrin, Ph.D.	Staff Fellow	CSL	DCRT
	B.S. Garra, M.D.	Staff Radiologist	DR	CC

COOPERATING UNITS (if any)

LAB/BRANCH
Computer Systems Laboratory

SECTION
Systems Design Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.6	0.6	0.0

Medical Image Data Compression

This project is concerned with the minimization of the number of information carrying units used to represent a medical image in order to improve the efficiency of transmission and storage of such images. Various image data compression techniques and their application to medical images are being evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques suitable to the clinical environment are being investigated.

Background and Objectives: Recently, there has been an increase in the number of medical imaging techniques that result in a digital image representation including computed tomography, nuclear medicine, positron emission tomography, ultrasonography, nuclear magnetic resonance, and digital radiography. As a result of this increased number of digital images, there is a need for Picture Archive and Communication Systems (PACS) that are capable of storing, transmitting, and displaying such images. Because the quantities of image data are large, it is important to consider techniques for data compression to reduce archival storage requirements as well as transmission rate constraints.

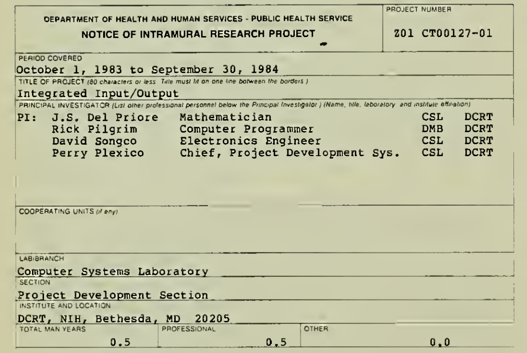
Progress in FY84: The formation of a medical image data base that will be used for testing data compression algorithms was started on the DCRT Image Processing Facility using images obtained from the Diagnostic Radiology Department of the Clinical Center. This included the digitization of x-rays with the facility's microdensitometer and the conversion of computed tomography images obtained from a General Electric scanner to a format suitable for processing on the DEC VAX computer system. The entropy of these images was calculated in order to obtain a theoretical bound on the maximum compression ratio that may be obtained with noiseless data compression techniques.

The entropy of an image is a mathematical formula, based on the pixel values of the image, which gives the limit to which an image can be compressed without compromising the data. A sample body CT image, in which each pixel contains 12 bits of information, had an entropy of 7.59 when the raw data was used, and an entropy of 5.97 when the first order difference (each pixel is subtracted from the one next to it and the difference is stored) was used. Thus, the maximum noiseless compression of that image was approximately 2:1.

The image data compression algorithms that have been published in the literature were reviewed and consist of the following three categories: Predictive Coding, Transform Coding, and Noiseless Coding. Transform Coding was chosen for implementation as this type of coding has the largest potential compression ratio. In particular, the Hadamard and Discrete Cosine transform techniques were selected because the Hadamard is one of the most computationally efficiently transform methods to implement and the Discrete Cosine, while requiring more time to compute, is close to being an optimal transform method that also has a reasonably fast computational algorithm. Noiseless Coding techniques were also chosen for implementation as these can be used on the coefficients obtained from the Transform Coding methods to further compress the image. A redundancy elimination algorithm, which replaces long strings of identical data with a three-word code, has been implemented.

Significance to Biomedical Research: The results of this project will be used in a PACS for the Clinical Center, NIH, and can benefit any medical center that needs to store and transmit a large number of medical images.

Proposed Course: The medical image data base will be expanded with more computed tomography and x-ray images and the addition of ultrasound images. Using the DCRT Image Processing Facility and the constructed data base, the Transform Coding methods will be implemented and evaluated with regard to the amount of compression attained and the quality of the reconstructed image. Methods for implementing these techniques suitable to the clinical environment will be developed with consideration given to the time required for compression and decompression.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00127-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Integrated Input/Output

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.S. Del Priore	Mathematician	CSL	DCRT
	Rick Pilgrim	Computer Programmer	DMB	DCRT
	David Songco	Electronics Engineer	CSL	DCRT
	Perry Plexico	Chief, Project Development Sys.	CSL	DCRT

COOPERATING UNITS *(if any)*

LAB/BRANCH
Computer Systems Laboratory

SECTION
Project Development Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.5	0.5	0.0

Integrated Input/Output

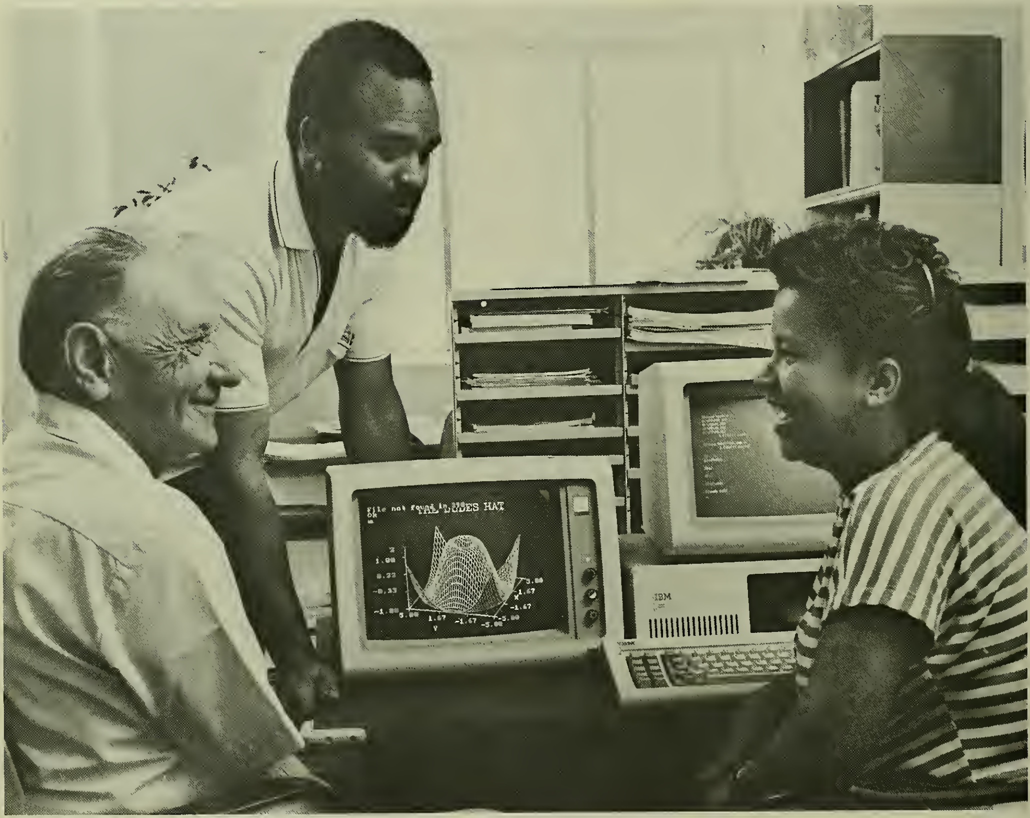
The Integrated Input/Output project is an attempt to expand the user interface of a personal computer from the usual keyboard input and CRT display to include more friendly and efficient modalities of communication. CSL efforts on this project include the development and modification of hardware and software to support desirable interface features like speech recognition and voice response, bar code interpretation, touch-sensitive CRT screens, and graphics input devices.

Background and Objectives: This project complements earlier CSL work to develop a Voice Output Terminal for blind computer users. The current trend toward widespread use of personal computers will lead to a need for many different input and output methods to suit users' requirements. The goal of the integrated input/output project is to provide user friendly interaction in a variety of complex human-machine environments. This requires the development of tools and concepts necessary to apply personal computer technology to applications ranging from laboratory research, where the user is occupied with the manual task of operating sophisticated instrumentation, to handicapped users' environments, where sight, hearing, or neuromuscular impairment must be overcome.

Progress in FY84: The first phase of this project has been to aid blind computer users by developing a voice recognition system that will allow a handicapped person to use a computer by voice command, without using a keyboard. In collaboration with a DCRT, DMB computer programmer who is a quadriplegic, we have designed and currently are developing a Voice Activated Shell to let him program his own personal workstation (IBM PC) by voice, and moreover, communicate through his PC to other computer facilities like the DCRT central systems.

Hardware for voice input and output on the IBM PC, and for touchscreen and bar code input (to accomodate future phases of the project), has been designed and is being developed by a contractor.

Proposed Course: After completion of the voice input system for handicapped users, we expect to develop ways of using other input/output devices, such as the ones mentioned above, in a way that fully parallels the keyboard and CRT display facilities of the PC but yet is "transparent" to the computer's operating system.



The Laboratory of Statistical and Mathematical Methodology supports NIH activities with statistical and mathematical help in the canalysis of biomedical data (left to right): Dr. Milos Pacak, Clark Collins, and Lisa Hawkins.

Laboratory of Statistical and Mathematical Methodology

James E. Mosimann, Chief

LSM activities can be divided into three areas: computation, consultation, and research.

Computation

A major part of LSM activity is the offering of statistical and mathematical systems/packages to the NIH user community. LSM accepts responsibility for evaluation of new program packages and their suitability for NIH. When LSM does support a system/package for the NIH community, it provides maintenance, documentation, instruction, and assistance for users to interpret the results.

Statistical Systems/Packages Support. During this year, the Statistical Software Section of LSM maintained the following program packages and programs:

- BMD, BMDP: Biomedical Computer Programs, UCLA.
- SPSS, SPSS-X, SCSS: Statistical Package for the Social Sciences, SPSS, Inc.
- SAS, SAS/GRAPH, SAS/ETS: Statistical Analysis System, SAS Institute, Inc.
- P-STAT: Statistical Package, P-STAT, Inc.
- IMSL: International Mathematical and Statistical Libraries, IMSL, Inc.
- MSTAT1: Collection of Mathematical and Statistical Programs, DCRT.

During the year SAS, SPSS-X, BMPD, PSTAT, IMSL, and MSTAT1 went through a major update. The SSS staff answered over 8,000 calls for assistance, and taught a total of 12 courses on these systems/packages; 2 each on the SPSS and BMDP packages and 8 courses on the SAS system.

The use of program packages continues to increase. The average accesses per month of all the statistical packages rose from around 63,000 during FY83 to over 74,000 in FY84. SAS averages over 67,000 accesses per month, up from 54,000 per month in FY83.

The average number of accesses per month for SPSS and SPSS-X was around 5,000, up from 4,600 in FY83. The average combined accesses per month (excluding SAS calls) of the BMDP and BMD packages was 1,800, down from 2,500 in FY83. Accesses to the IMSL and MSTAT1 packages cannot be counted, but it is estimated that usage increased during FY84.

Support for MLAB. The Biomathematics and Computer Science Section maintains the DECsystem-10 interpretive program MLAB, a package designed and implemented by BCS staff. During FY84, several hundred biomedical researchers at NIH used this package for modeling and graphical display tasks. MLAB is used in the NIH-funded Prophet system, the SUMEX-AIM system at Stanford University, and the NIH-EPA Chemical Information System. It has been distributed to universities and research centers at their request.

During FY84, BCS augmented MLAB by addition of eigenvalue and eigenvector computation routines, and by routines for graphical shading of polygons. Two advanced and two introductory courses were taught for MLAB. Two articles on MLAB and C-LAB techniques appeared in *INTERFACE*. The second edition of the *MLAB Beginners Guide* was distributed. A quick-reference pamphlet, the *MLAB Reference Handbook*, was prepared and is now being printed. The incorporation of the C-LAB system into MLAB was completed, and a C-LAB Applications Manual was published.

Support for the GRAPH System. Major improvements were made to the DECsystem-10 software system GRAPH, which produces publication-quality graphics with a minimum of work. New features added include horizontal bar graphs, graphs with broken axes, and joystick control of the placement of titles. A new manual was published, describing the GRAPH system in detail.

Support for Other Software. BCS continues to maintain certain special-purpose software and to give limited assistance to users upon request. Version 3.0 of the REDUCE program was received from the Rand Corporation. It will be released when testing and document preparation are complete. This program facilitates symbolic computation for algebraic expressions or matrices.

A program developed by BCS for interactive construction of an index for a document file has been supported. Various LSM-created programs for analysis and reconstruction of biological shapes using the symmetric axis method have been supported. Due to the departure of the system developer during FY84, BCS discontinued support of the Unified Generators package. The PROLOG system support was transferred to MIS, LSM.

Consultation

As in previous years there was considerable variation in the amount of time required for an LSM consultation. Some very brief consultations are successful and are brief precisely because there is a known answer to the question posed. Other consultations involve extensive time and statistical/mathematical/computer science research as well.

LSM consultations in FY84 were of tbe following types:

- Mathematical, statistical and computer science advice with limited computer use (5 percent)
- Mathematical or statistical advice with considerable computer use (55 percent)
- Computational advice alone (40 percent).

The large computer use in these figures results from the continued availability and use of general purpose statistical and mathematical packages like SAS and MLAB. These percentages are unchanged from last year.

The diverse nature of LSM consulting is indicated by the projects and activities listed below.

Clinical Research, Patient Care, Epidemiology

Gastrointestinal Diagnostic Study. M. Spiegel, R. Johannes (Johns Hopkins Medical School). Responses were obtained for 20 questions asked of 145 patients with gastrointestinal problems. The purpose was to determine whether any subset of the answers could be used as diagnostic aids, so that an extensive examination could be avoided. LSM assisted in discriminant analysis of the data.

Precocious Puberty Study. G. Cutler (NICHD/DE). A study of precocious puberty in children examined the differences and relatedness of several dependent variables (e.g., adrenal androgens, cortisol) given the cross-classification of the population into normal, precocious puberty, and hypogonadism. LSM provided advice and assistance in statistical evaluation using unbalanced analysis of variance and covariance.

Catacholomine Levels in Pathology. E. Lack (NCI/DCBD/LP). From autopsies, levels of dopamine and norepinephrine are obtained from normal patients, sudden infant death syndrome patients, cystic fibrosis patients, and patients with cyonotic congenital heart disease. LSM developed an analysis of covariance model to study differences in catacholomine levels in the four groups, controlling for age.

Proteins in Multiple Sclerosis. M. Harrington (NIMH/LCS). Protein content in the cerebrospinal fluid of patients with multiple sclerosis and other neurological diseases is studied with two-dimensional electrophoresis gels. LSM provided a statistical model to discriminate MS patients versus normal patients and patients with other neurological diseases based on the protein content.

ACTH Binding in Pathological Brain Tissue. C. Kaufmann (NIMH/OSMR). Comparative binding of ACTH was studied in pathological tissue samples from suicide victims and controls. This analysis was part of a study of chemical properties of depression. LSM provided assistance with mathematical modeling.

Laboratory Investigation

Evolution of Fibrinogen Gene. G. Crabtree (NCI/DCBD/LP). Probabilistic models for the evolution of three present-day forms of the fibrinogen gene were analyzed. The basic model holds that elimination of introns over time was completely random, from some unknown original number of introns. LSM provided advice on use of a minimum chi-square-like technique to conclude that the random elimination model was improbable, so that other forces of intron loss were necessarily at work.

Effects of Benzo(a)pyrene on Ovarian Function. E. Sibergeld, D. Mattison (NICHHD/PR). Effects of benzo(a)pyrene (BP) on murine ovarian function and fertility were studied. BP is a common pollutant that has been implicated as a reproductive toxin. Experiments explored effects of a single exposure to BP on the ability of the ovary to ovulate and to form corpora lutea. LSM provided assistance in the use of nonparametric analyses and multiple comparisons, and also a nonparametric test against ordered alternatives.

Blood Platelets. J. Fratantoni (BB/DBBP). Blood platelets from stored whole blood and from pheresis are studied at a fixed time and storage temperature. A model has been developed by LSM to relate platelet counts to pH level, whole blood cell count, and volume of blood stored.

Brain Edema in Rabbits. T. Kuroiwa and R. Cahn (NINCDS/LNNS). The water content is being investigated in brain tissue of rabbits that have been subjected to a hypertensive insult that breaches the blood brain barrier. A model was developed by LSM that predicts specific gravity of grey and white brain tissue based on the amount of extravasated serum albumen present at varied times after the insult.

Atherosclerosis in Swine. H. Kruth and J. Cupp (NHLBI/IR/EA). Effects of high cholesterol/lard diets in swine are assessed by sacrifice of the animal followed by counts of single cell suspension of foam cells from the aorta using flow cytometry. LSM provided statistical advice in the design and the analysis of linear models that test for differences in the diets, adjusting for the litter effect in the experiment.

Brain Tissue Analysis. M. Litzinger and P. Nelson (NICHD/NPM). Competitive binding of neuroblockers and acetylcholine at synaptic sites of brain tissue was studied. LSM provided modeling assistance and assistance in use of MLAB.

Tri-Ligand Binding Model. A. Minton (NIADDK/LBP). A theoretical model of tri-ligand binding was formulated to provide an alternate explanation for reported experiments, in reviewing a scientific paper. Using MLAB, LSM assisted in formulating a mathematical model and analysis of the model.

Optical Dichroism Response. A. Stone (NIMH/LNB). LSM assisted in designing and evaluating models designed to predict structural properties of protein molecules by analysis of optical dichroism data.

Graphical Display of Amino Acid Properties. R. Guy (NCI/DCBD). LSM provided assistance in graphical display of the properties of a mathematical model showing energy needed for movement of amino acids from a water to a lipid environment.

Program Management and Administration

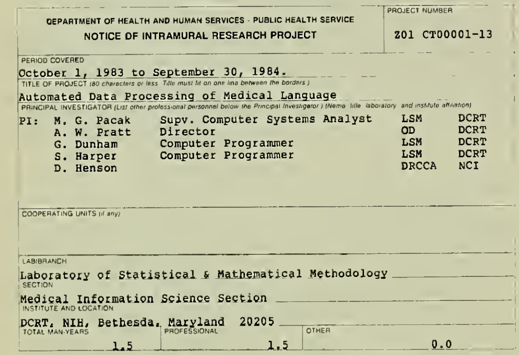
Clinical versus Basic Research Grant Applications. J. Cuca (DRG/DIR). Data is collected on NIH R01 research grant applications categorized by type of research (clinical or basic) and type of study section (clinical or basic), as well as a detailed categorization of shortcomings in grant applications. LSM provided a contingency table analysis of differences in these categories, in approval rates and in priority scores differences in the various categories.

Computer Research and Technique Development

Poster Display. R. Brooks (NINCDS/IR/SN). LSM provided assistance in generating computer displays of surfaces in three-dimensional space, representing a mathematical model.

MLAB Procedure Resumption. R. Hendler (NHLBI/LB). LSM devised a technique by which an MLAB procedure could be interrupted for execution of as many typed MLAB commands as desired, after which the user could resume processing the procedure from the point of interruption.

Research Projects



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00001-13

PERIOD COVERED
October 1, 1983 to September 30, 1984.

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Automated Data Processing of Medical Language

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. G. Pacak	Supv. Computer Systems Analyst	LSM	DCRT
	A. W. Pratt	Director	OD	DCRT
	G. Dunham	Computer Programmer	LSM	DCRT
	S. Harper	Computer Programmer	LSM	DCRT
	D. Henson		DRCCA	NCI

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical & Mathematical Methodology

SECTION
Medical Information Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.5	1.5	0.0

Automated Data Processing of Medical Language

Research in medical linguistics continued, including development of a comprehensive lexicographic data base, modeling of categorized nomenclatures using partially ordered sets, study of diagnostic noun phrase syntax, and a collaborative effort to develop a computerized dictionary of the vocabulary of pathological lymphoma reports.

Collaboration continued with the Laboratory of Pathology, NCI, and the DCRT Data Managment Branch to maintain and improve the data base of Clinical Center surgical pathology reports.

The automatic encoding system provided by MIS computes a representation of the summary diagnoses of the surgical pathology report as written by the pathologist, in a language based on the vocabulary of the Systematized Nomenclature of Pathology (SNOP-NIH). Statements in this representation language convey the site and tissue of the specimen, the specific morphologic and histopathologic diagnoses, and etiologic agents involved in a diagnosis.

Continued collaboration with Dr. Donald E. Henson, NCI (Division of Cancer Prevention and Control, Organ Systems Branch), has been basic to this work. We have begun work on specific areas of the dictionary along the lines established for the lymphoma vocabulary with interested specialized pathologists including Dr. Elaine S. Jaffe, NCI (Division of Cancer Biology and Diagnosis, Laboratory of Pathology, Hematopathology Section).

Work has continued on the creation of a comprehensive lexicographic data base relating the body of medical nomenclature and vocabulary to itself in various logical ways, and to existing structuring or coding systems. The goals are: to produce the semi-automatic display of significant relationships of one dictionary system to another, to merge dictionaries, and to maintain and extract special purpose microglossaries necessary for medical language processing and data base organization.

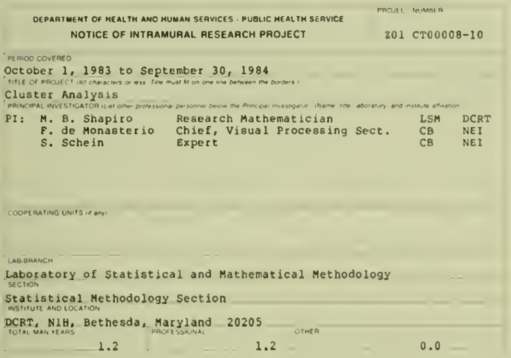
A study introducing the partially ordered set as a general mathematical model for categorized nomenclatures, was accepted for publication in *Methods of Information in Medicine*

A theory of syntax for computational processing of diagnostic noun phrases was developed and presented at the New York University Workshop on Sublanguage.

Publications:

Dunham, G. D.: The Role of Syntax in the Sublanguage of Medical Diagnostic Statements. Conference on Sublanguages, NY University, January 1984 (in press).

Dunham, G. S., Henson, D. E., and Pacak, M. G.: Three Solutions to Problems of Categorized Medical Nomenclatures. Linguistic String Project, Courant Institute-NYU, 1984 (in press).



PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CT00008-10

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cluster Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. B. Shapiro	Research Mathematician	LSM	DCRT
	F. de Monasterio	Chief, Visual Processing Sect.	CB	NEI
	S. Schein	Expert	CB	NEI

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology

SECTION

Statistical Methodology Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20205

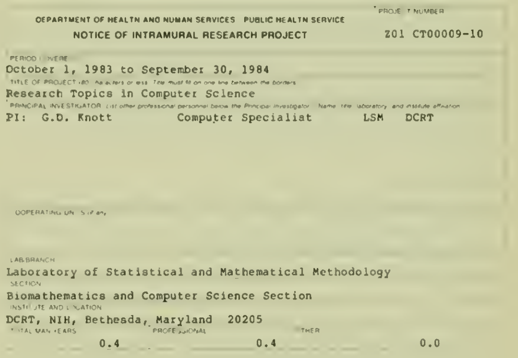
TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.2	1.2	0.0

Cluster Analysis

The main objective of this project is the application of computer cluster analysis and related methods to NIH research problems.

Algorithms for analyzing spatial point patterns were developed for testing patterns of retinal cones for regularity. The incorporation of C-LAB into MLAB was completed, and the results of clustering method studies were made available to NIH researchers by publication of a C-LAB Applications Manual.

Work continued on analyzing the spatial point patterns of retinal cones. A major revision was made on the paper, "Regularity and Structure of the Spatial Pattern of Blue Cones of Macaque Retina," which was resubmitted to the *Journal of the American Statistical Association* for publication. The analysis was redone using a jackknifing technique for evaluating the fit of the various models tried.



PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CT00009-10

PERIOD COVERED

October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Research Topics in Computer Science

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G.D. Knott	Computer Specialist	LSM	DCRT

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Statistical and Mathematical Methodology

SECTION

Biomathematics and Computer Science Section

INSTITUTE AND LOCATION

DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.4	0.4	0.0

Research Topics in Computer Science

Various storage and retrieval algorithms have been studied. The development of flexible and efficient storage and retrieval algorithms is very useful, because such algorithms are used in almost all computer programs. Thus biomedical computation in particular can benefit from improved storage and retrieval methods.

Currently, a study of hashing storage and retrieval methods is underway. This has resulted in an analysis of the performance of the hashing methods that resolves collisions using direct-chaining with and without coalescing lists. Progress has been made on analyzing the insertion cost for direct-chaining, involving the computation of a hard-to-derive covariance.

The object of this project is to develop theoretical bases for new computer methods that will expand and improve the use of computing in biomedical computation. The methods used are the application of known algorithms and the development of new pertinent theorems involving combinatoric and other related mathematics. Research work in storage and retrieval algorithms and their efficiency has been the primary topic of concern.

An algorithm for storage and retrieval using hashing with direct-chaining, where lists coalesce as items are stored, has continued to be developed and analyzed. This version involves inserting items at the heads of their various subchains rather than at the tails, so it has been called the method of early-insertion coalescing lists. Analysis of the method involves several intricate sums. A paper was prepared for this method, and also a joint paper analyzing the basic direct-chaining method.

Publications:

Knott, G. D.: A Language for Modeling and an MLAB Example: Multiple-Site Binding Analysis. U.S. Public Health Service Professional Association, 19th Annual Meeting, June 3-6, 1984, pp. 458-462.

Knott, G. D.: Direct Chaining with Coalescing Lists. *J. Algorithms* 5 (1): 7-21, 1984.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00011-10

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Discrete Mathematics and Applications

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Hutchinson	Supv. Res. Mathematician	LSM	DCRT

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Biomathematics and Computer Science Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.7	0.7	0.0

Discrete Mathematics and Applications

Inclusion relations between vector spaces and related problems concerning modules over rings were studied.

Preparation of scientific manuscripts by computer graphics methods using printer-plotters and laser printers was investigated.

The project objective is to develop mathematical theory and computational techniques using discrete mathematics (algebra, combinatorics, and graph theory), and to apply such methods to problems of biomedical research and computer science.

The study of algebraic structure of submodules of module products M x M was completed, and a manuscript submitted for publication. Additional results were obtained in axiomatization of varieties of relation algebras related to these module product algebras.

Systems for input of scientific text were studied, and a preliminary design was made for use with the IBM 6670 laser printer. A pilot program was developed under contract to LSM realizing this design. Further development of the pilot program into an expanded version is underway. This effort includes construction of fonts appropriate to scientific text needs at NIH.

Proposed Course:

Study of module theory will continue, in particular the search for general representations of relation algebras.

Software realizing the input system for scientific text will be prepared and offered to the NIH user community, for use with the IBM 6670. More general and flexible designs are under consideration using the NIH8188 and Tektronix 4114. When the IBM 3800-III laser printer becomes available at NIH, adaptation of the design for use with this device is also planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00013-10

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Multivariate Statistical Analysis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.E. Mosimann	Chief	LSM DCRT
	J. N. Darroch		Flinders Univ., Adelaide, Australia
	D. Meeter	Professor	Florida State Univ., Tallahassee
	D. F. Sinclair		CSIRO, Aitkenvale, Australia

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Office of the Chief

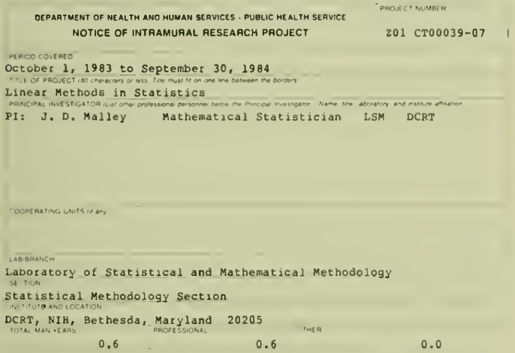
INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.3	0.3	0.0

Multivariate Statistical Analysis

The objective of this ongoing project is the study of multivariate ratios or proportions.

Study continued on multivariate statistical methods for analyzing ratios that follow a multivariate lognormal distribution. Specialized programs for the analysis of proportions and ratios have been prepared. Studies of random proportions that follow mixtures of Dirichlet distributions have been undertaken. The principal investigator organized an invited papers session on this topic for the XII International Biometric Conference held in Tokyo, Japan, September 2-8, 1984.


DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00039-07

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Linear Methods in Statistics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: J. D. Malley Mathematical Statistician LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Statistical Methodology Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.6	0.6	0.0

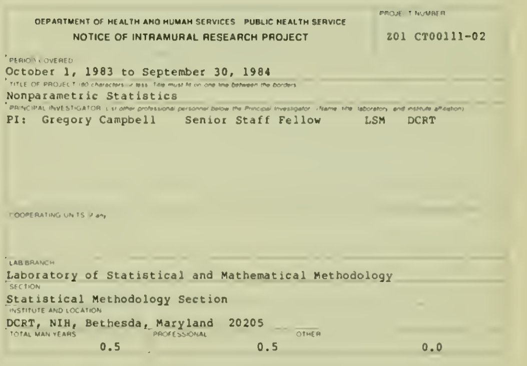
Linear Methods in Statistics

Linear methods in statistics as applied to biomedical data analysis continue to be studied. In particular, the problem of finding optimal estimates for variance components has been essentially solved, using methods of linear models. This problem had been outstanding in the field for nearly thirty years. Three papers have been written on this problem, and the first fundamental one has been accepted for publication.

The solution was unexpected and at places seemed to violate certain known results on the problem. However, these were shown to be largely compatible with the results we have obtained and at other places in error. Moreover, the collection of basic results on which the optimal solutions were based have themselves been studied, leading to several corrections of the existing literature and a new vastly simpler proof of the main basic theorem.

Publications:

Malley, J.D.: Optimal Estimates for Variance Components. *J. Multivariate Analysis* (in press).


DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00111-02

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Nonparametric Statistics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: Gregory Campbell Senior Staff Fellow LSM DCRT

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Statistical and Mathematical Methodology

SECTION
Statistical Methodology Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.5	0.5	0.0

Nonparametric Statistics

Research is concentrated on several topics of nonparametric statistics. The study of nonparametric multiple comparisons was continued in FY84, with particular attention to the theoretical as well as computer simulated behavior of various procedures. The optimal selection of a sequence of items based on relative ranks with ties has been investigated. Thirdly, an evaluation of tests for correlated proportions with incomplete data is continuing.

Research is concentrated in several areas of nonparametric statistics with applications to biomedicine. The development and comparison of multiple comparison procedures continues. Stepwise nonparametric methods of concluding differences among treatments have been investigated theoretically, using computer simulations. A paper (with J.H. Skillings) has been submitted.

Further work on a new approach is ongoing. The development of distribution-free techniques for data to which weights have been attached is being investigated. The computer-generated exact distribution and the large-sample theory are of interest. The weights arise in the biomedical setting through covariate information or as probabilities of other events.

The research area of proportions is also under investigation. A paper on incomplete correlated proportions has been accepted for publications. Further work is ongoing on the covariance structure of proportions.

Publications:

Campbell, G: Optimal Selection Based on Relative Ranks of a Sequence with Ties. *Advances in Applied Probability* 16: 131-146, 1984.

Campbell, G.: Testing Equality of Proportions with Incomplete Correlated Data (Incomplete Correlated Proportions). *J. of Statistical Planning and Inference* (in press).

Santner, J. S., and Campbell, G.: A Constant Amplitude Fatigue Study of an Aluminum Powder Metallurgy Alloy. *J. Testing and Evaluation* II: 333-339, 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00120-01
PERIOD COVERED May 14, 1984 to September 30, 1984		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Computer Graphics and Mathematical Applications		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) PI: K. R. Bhutani Visiting Associate LSM DCRT		
COOPERATING UNITS (if any)		
LAB/BRANCH Laboratory of Statistical and Mathematical Methodology		
SECTION Biomathematics and Computer Science Section		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Maryland 20205		
TOTAL MAN-YEARS 0.3	PROFESSIONAL 0.3	OTHER 0.0

Computer Graphics and Mathematical Applications

The notion of completeness of Boolean algebras in topos of sheaves on a locale was studied. Preparation for computer graphics research is continuing.

Project Objective:

The purpose is to carry out study in the areas of algebra (abelian groups, Boolean algebras, rings and modules) and computer science and to develop techniques to apply the theory for solving problems of biomedical research. This will include development of algorithms and programs for use with an intelligent graphics terminal together with various software systems for graphical display of biomedical data.

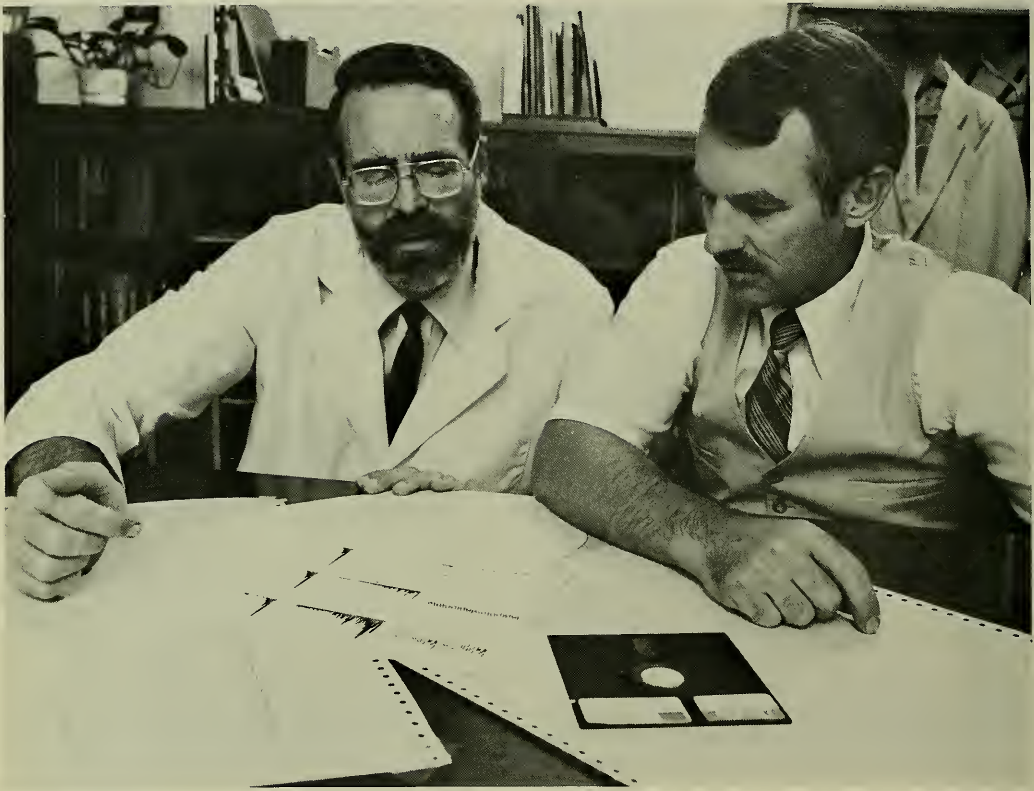
A study of the notion of completeness in the category of Boolean algebras in a topos of sheaves on a locale was begun. One was interested to find out if complete is the same as injective in this category. For any lattice in a topos of sheaves on a locale, we first show that its lattice of ideals is complete. Using this the completeness of the lattice of normal ideals is obtained. This will be further used in showing that every Boolean algebra in sheaves on a locale has a complete essential extension. Finally one aims to show that complete is the same as injective.

Review of existing software is continuing in preparation for computer graphics research and development.

Proposed Course:

Research and documentation of previous work in Boolean algebras will continue.

Activity in computer graphics research will be primarily directed towards making computer generation of graphs faster and more flexible by using the capabilities of intelligent graphics terminals to simplify mainframe computation.



The Laboratory of Applied Studies engages in collaborative projects in basic and clinical biomedical science. Dr. James Bailey (left) heads the Medical Applications Section; Acting Lab Chief Dr. John Fletcher heads the Applied Mathematics Section.

Laboratory of Applied Studies

John E. Fletcher, Ph.D., Acting Chief

Clinical Research and Patient Care

Computer-based studies of physiology and pathophysiology during exercise. R. Burgess, M. Horton, E. Pottala, J. Bailey (LAS); A. Nienhuis, R. Crystal (NHLBI). In this project, breath-by-breath analyses of pulmonary gas exchange performed by a laboratory minicomputer-based system are the bases for studies of oxygen delivery to tissue in normal states and in pulmonary, cardiovascular, and hematologic pathophysiologies.

Serial testing of a patient during bicycle or treadmill exercise provides objective indications of severity of disease and efficacy of treatment. Half of a protocol for studying drug therapy in patients with sickle cell disease was completed, and testing of patients with idiopathic pulmonary fibrosis and alpha-1-antitrypsin deficiency began.

Computer-based method of monitoring central nervous system function in critically ill patients. R. Burgess, M. Horton, E. Pottala, J. Bailey (LAS); C. Natanson, J. Parrillo (CC). The goal of this project is to develop a microcomputer-based system for analysis and display of scalp-recorded neuroelectrophysiological signals following programmed stimuli (i.e., evoked potentials).

The combination of a custom hardware configuration and high speed signal analysis algorithms permit physicians to make timely assessments of changes in the CNS of critically ill patients. Interfacing of the digital controllers to the computer was completed, and fabrication of the analog preprocessor is underway.

Computer systems for nuclear medicine. M. Douglas, J. Bailey (LAS); S. Bacharach, et. al., (CC, Nuclear Medicine); R. Bonow (NHLBI). This project involves development and application of computer methods to such diagnostic imaging activities as ECG-gated radionuclide ventriculography and dynamic scintigraphic studies of other organs (e.g., kidneys, lungs).

Extensive studies of more than 60 parameters in radionuclide ventriculography have shown that only 12 parameters were potentially useful in separating cases with regional wall motion. The method for automatic gallium index in lung scans has been successfully applied to 19 cases. The IBM PC XT graphic and imaging capabilities have been found useful for functional images but inadequate for other images. New studies began in tumor imaging with monoclonal antibodies and PET.

Computer analysis of electrocardiograms. J. Bailey, M. Horton (LAS); D. Savage, S. Palmeri (NHLBI); L. Jackson (Georgetown University Medical Center). The continuing goals of this project have been to evaluate the diagnostic power and epidemiological utility of the leading computer programs for ECG interpretation. ECG data on several thousand cases from the Framingham study have been collected. Of these, five to six percent have echocardiographic evidence for left ventricular hypertrophy.

Only 80 percent of the cases that expert readers said met the ECG criteria for LVH, clearly had LVH by echo exam; another 3 to 4 percent were borderline; the remainder (about 16 percent false positives) could not be explained. The IBM program made many more false positive diagnoses with about the same sensitivity as the expert readers. The IBM program relies heavily upon QRS amplitude whereas the readers make better use of ST-T changes. Whether this entirely explains the discrepancy between IBM and the readers is currently under study. After an 18-month delay the simultaneous 12-lead data has begun to arrive from Georgetown so that a comparison of IBM and Marquette analysis techniques can proceed.

Laboratory Investigations

Computer analysis of electron and x-ray micrographs. M. Douglas, J. Bailey (LAS); J. Costa (NIMH). This project involves the development and implementation of mathematical models and image enhancement techniques to analyze computer-acquired information from electron energy-loss and x-ray spectra indicating the location of extremely small quantities of important chemical elements and active protein molecules within cells.

Examination of mass thickness of dense bodies in platelets reveals that absolute mass thickness is not correlated with diameter, suggesting that the total amount of calcium and phosphates comprising the dense body achieves a relatively constant concentration, regardless of the surface area available for accumulation. This is consistent with other observations that the core exists in the form of an amorphous solid.

The computerized model reveals differences of at least 20 percent in average mass thickness of two populations of dense bodies. Incubation of platelets with iodoquine increases the mass thickness about 25 percent, which is consistent with previous data suggesting quinacrine accumulation in dense bodies.

Analysis of physiologic signals. E. Pottala, H. Le, J. Bailey (LAS); J. Dvorak (NIAID); M. Postan (WHO); W. van Arsdel (FDA). This project uses the LAS minicomputer system (MAC-16) for analysis of biological signals (ECG, EMG, EEG, etc.). This year, methods for acquiring and analyzing rodent ECG's were improved so that new animal models of drug-induced cardiotoxicity (FDA) and myocardial infections (NIAID, WHO) could be more effectively studied.

Mathematical modeling of biological processes. J. Fletcher (LAS); R. Schubert (Lousiana Tech. Univ.). Quantitative models that describe the relationships between free and facilitated substrate diffusion, metabolism, and microcirculatory flow are being developed and evaluated.

These models can identify the critical physiological parameters for substrate supply to tissue and their ranges in normal and pathophysiological states. Exploration of a new unified model for perfused organ experiments has been completed. Limits of capillary wall permeabilities were explored and the details of coupling effects were elucidated.

Network modeling in biology. B. Bunow, E. Pottala (LAS); T. Colburn (NIMH); and other NIH, FDA, and NIOSH scientists. LAS has shown that network simulation languages (e.g., NET2, SPICE), operating on NIH central computers and VAX sytems at NIMH, NCI, and NIADDK, provide a powerful modeling tool for NIH scientists who are modeling neural, electromechanical, and biochemical systems. Models constructed during FY83 were parametrically explored during limited activity in FY84.

Active transport, biochemical kinetics, and their interactions. B. Bunow (LAS); D. Mikulecky (Medical College of Virginia); J. Kernevez (Univ. of Tech., Compiegne, France); R. Hendler (NHLBI). This project examines experimental and mathematical studies of kinetics and thermodynamics of biological processes involving enzyme-catalyzed reactions.

Thermodynamic principles and mathematical analysis were applied, in collaboration with NIH scientists, to problems in membrane transport, bioenergetics, and ligand binding. A kinetic description of simultaneous reaction and transport has been developed that shows the inadequacy of previous irreversible thermodynamic approaches.

Computer Research and Software Development

Mathematical and computational methods for solving nonlinear equations. R. Shrager (LAS); R. Hendler, R. Kincaid (NHLBI); B. Kamgar-Parsi (LAS). In FY84, papers on finding zeros of a function and on analyzing titration spectra by singular value decomposition were published. Newly-developed minimization procedures for unconstrained and linearly constrained problems have been coded; and digital filters with exact coefficients are being developed for data from cell respiration and for a new type of mass spectrometer. A stable method for solving simultaneous nonlinear equations is under development. Current applications include cytochrome potentials, calmodulin-calcium-manganese interactions, and protein folding studies.

Numerical methods for the solution of mathematical models describing reaction-diffusion and other processes in biological systems. M. Bieterman, J.E. Fletcher (LAS); I. Babuska (University of Maryland). This project is concerned with the investigation, development, and implementation of computer methods for the solution of systems of ordinary and partial differential equations that are used to model dynamic physiological processes.

Adaptive finite element techniques have been generalized and used for models of nerve conduction, oxygen transport in tissue, uptake of macromolecules into the lymphatic system, and in preliminary studies of subsurface contaminant flow. FORTRAN coded packages implementing these and other techniques are available for use on the major DCRT computers.

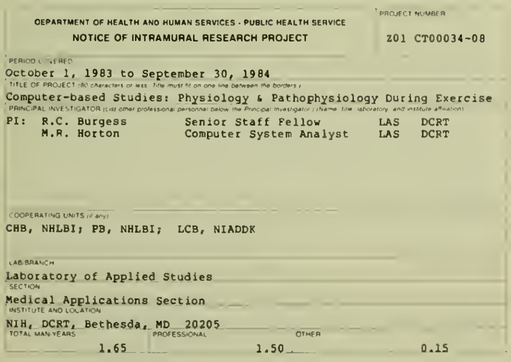
Applications of personal computers to laboratory research. M. Horton, R. Burgess, M. Douglas, E. Pottala, B. Bunow, R. Shrager, H. Le (LAS); Personal Workstation Project (DCRT). The goals of this project are to determine the applicability of personal computer-based systems in research laboratories, to assemble such systems, and to test them in laboratory investigations.

Three PC-based systems have been assembled, each with the internal boards, special peripheral equipment, and appropriate software, to function in one of three common laboratory research activities:

1. laboratory realtime data acquisition and anaylsis,
2. physiological imaging, and
3. mathematical modeling and numerical analysis.

Evaluation began of various software and hardware products.

Research Projects



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00034-08

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Computer-based Studies: Physiology & Pathophysiology During Exercise

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R.C. Burgess	Senior Staff Fellow	LAS	DCRT
	M.R. Horton	Computer System Analyst	LAS	DCRT

COOPERATING UNITS (if any)
CHB, NHLBI; PB, NHLBI; LCB, NIADDK

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
NIH, DCRT, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.65	1.50	0.15

Computer-based Studies of Physiology and Pathophysiology During Exercise

This project, through a collaborative effort of LAS with the Clinical Hematology and Pulmonary Branches of NHLBI, is directed toward a deeper understanding of the physiology and pathophysiology of oxygen transport to tissues and the development of a clinical tool with a high degree of sensitivity, through the use of computerized breath-by-breath analysis of gas exchange and computer-based models of ventilation and oxygen transport.

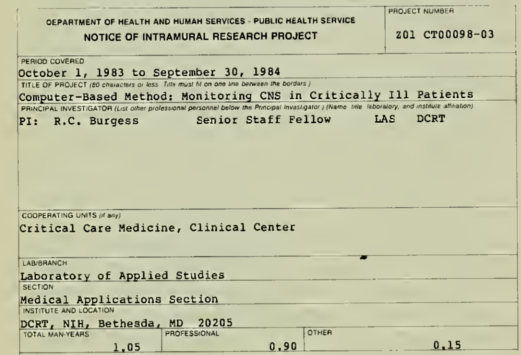
Progress During FY84: A comprehensive computerized exercise laboratory with realtime capability for simultaneous control of the exercise device (bicycle or treadmill); acquisition of multichannel respiratory and cardiovascular signals; and calculation of gas exchange parameters on a breath-by-breath basis were established.

Also developed was a versatile graphics package for video and hardcopy display of all measured and computed parameters. Calibration procedures have been refined and are now tracked using an IBM PC.

A study to evaluate the efficacy of Nifedipine in patients with sickle cell anemia is approximately half completed. Results of multifactorial exercise testing were employed as a measure of microcirculatory oxygen transport, and are being correlated with measurements from laser Doppler velocimetry, PET Scanning, and measurements from the opthalmic microvasculature. Preliminary testing of patients with idiopathic pulmonary fibrosis and alpha-1-antitrypsin deficiency has begun.

Proposed Course: Completion of the study of vasodilators in sickle cell patients is anticipated in FY85, and expanded studies with the Pulmonary Branch, NHLBI, will be undertaken. The exercise laboratory has been equipped to evaluate the improvement afforded by supplemental oxygen in patients with pulmonary dysfunction.

Further refinement of the hardware and software will be carried out during FY85 to: correlate exercise parameters with static pulmonary function tests; analyze ECG arrhythmias; reduce manual calibration procedures (e.g., using computer-operated solenoid valves to control test gas flow); and provide alternative graphical output formats.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00098-03

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Computer-Based Method: Monitoring CNS in Critically Ill Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: R.C. Burgess Senior Staff Fellow LAS DCRT

COOPERATING UNITS *(if any)*
Critical Care Medicine, Clinical Center

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.05	0.90	0.15

Computer Based Method of Monitoring the CNS in Critically Ill Patients

This project is a joint effort between the Laboratory of Applied Studies and the Department of Critical Care Medicine to design, build, and implement a highly clinically oriented, distributed-processing, microcomputer-based system for analysis and display of scalp-recorded neuroelectric signals. This tool will be used: to investigate the degree of dysfunction in neurologically impaired patients, to correlate the indices developed with other measures of cerebral function, and to evaluate the effectiveness of various therapeutic interventions.

Background and Objectives: In the critically ill patient with multiple organ dysfunction, impaired brain function frequently coincides with deterioration of other major systems. However, the degree of damage and capacity for restoration of the brain does not necessarily parallel that of the rest of the body. In addition, assessment of the central nervous system is hampered by limitations imposed by procedures (e.g., endotracheal intubation) and/or drugs (e.g., Pavulon).

The initial phase of this project is directed toward the development of a comprehensive, mobile, neurodiagnostic system including:

1. a precision analog front-end for low-noise detection, amplification, and filtering of the spontaneous and evoked EEG activity,
2. devices to deliver programmed, visual, auditory and somatosensory stimuli,
3. a central processor with intelligent peripherals for data acquisition, manipulation, calculation, and storage, and
4. a display capable of high resolution graphics and printout for presentation of current and past data, trends, and interpretive imaging.

After initial development and testing has been completed, the system will be used in the Critical Care Unit, Clinical Center, to address the following questions:

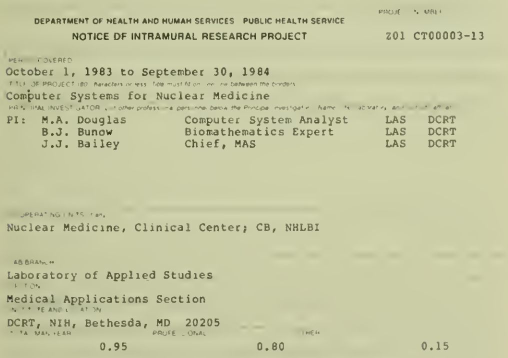
- Which electrophysiological parameters can be used to best follow the functional neurologic status of the patients?
- What is the optimal protocol for obtaining data in order to balance recording requirements and nursing care needs?
- How can the parameters best be combined into a meaningful profile and best be displayed to provide comprehensive, yet easy-to-assimilate clinical information?
- How does the information offered by this system compare to other neurodiagnostic techniques?
- How does this system improve care of the patient and understanding of the pathophysiologic dynamics?

Progress During FY84: A specialized mobile equipment rack containing the computer, array processor, front-end amplifier/filter, stimulation devices, and displays has been developed. The array processor has been updated with the purchase of new circuit boards and software from the manufacturer. Initial programs have been completed to enable operator entry of patient parameters.

Acquisition of noise-free, microvolt level signals from the patient's scalp in the electrically hostile environment of the Critical Care Unit is crucial to reliable semi-automatic monitoring of CNS function.

Design of a computer-controlled eight-channel amplifier/filter to allow automatic sequencing from one evoked potential mode to the next has been completed. A single channel prototype has been tested, and the engineering necessary to fabricate the modular multichannel system is underway. Four programs employing digital filtering to process the evoked potential signals have been developed.

Proposed Course: Testing and a refining of programs will be carried out when the data acquisition front-end has been completed. Programming segments performing extensive matrix calculations will be offloaded to the array processor to speed computation. This system will facilitate evaluation of multiple algorithms for extracting functional information from the electrophysiological data.



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 CT00003-13

October 1, 1983 to September 30, 1984

Computer Systems for Nuclear Medicine

PI:	M.A. Douglas	Computer System Analyst	LAS	DCRT
	B.J. Bunow	Biomathematics Expert	LAS	DCRT
	J.J. Bailey	Chief, MAS	LAS	DCRT

Nuclear Medicine, Clinical Center; CB, NHLBI

Laboratory of Applied Studies

Medical Applications Section

DCRT, NIH, Bethesda, MD 20205

0.95	0.80	0.15

Computer Systems for Nuclear Medicine

This project involves computer-based mathematical analysis, pattern recognition, and image processing in support of diagnostic activities in the Nuclear Medicine Department of the Clinical Center and collaborating Institutes. Applications include computerized ECG-gated radionuclide angiocardiography and myocardial perfusion scintigraphy, renal dynamics, tagged monoclonal antibody studies and pulmonary ventilation-perfusion relationships.

Progress During FY84:

Cardiac Scintigraphy: A study has been completed that tested more than 60 parameters for ability to detect abnormal cardiac contractility. Many parameters were found to be highly correlated, hence not independent, but were included in the study for completeness. In some cases two parameters might be highly correlated, but nevertheless significant, in those few cases where they disagreed (e.g., ejection fraction and filling fraction). A dozen parameters showed some potential for separating normal from abnormal cases and focal from diffuse abnormalities.

Whole Body Gallium: The goal of this project is to improve the quality and repeatability of the Gallium Index for lungs, which correlates with active inflammation.

Gallium Index in Lung Scan: To automate quantification of Gallium uptake by the lungs, a sample vial of a known quantity of Gallium was placed in the field of view. Automated delineation algorithms were developed for the sample vial, the whole body, a representative background area, a high-uptake region (generally liver) within the body, and a low-uptake region (generally bladder) within the body. Lungs are manually delineated with a light pen on the CRT. A Gallium Index is computed as a ratio of lung uptake to the range of uptake from the high to low uptake regions. The system was tested on 19 posterior view cases and comparison was made of its computed index versus the routine, visually estimated index. The system's index was generally successful at differentiating between normal lungs and those with abnormal regions. There was some positive correlation between the automated and visual indices; however, inspection of the cases revealed considerable variation in the visual evaluations obtained with different observers, and with different contrast settings on the display.

Desk top computers: There is a high demand for time on the current display devices used in nuclear medicine, all of which are in the same room. It would be useful to find an inexpensive means to distribute additional display capabilities. Use of the IBM PC XT was investigated for this purpose. The maximum available spatial resolution of 640 by 480 is inadequate for scientific graphics; the gray scale and color scale depth also is insufficient for such imaging as ventriculograms. However, PC XT compatible devices with 640 by 480 resolution and 16 simultaneous colors from a palette of 4096 can be an appropriate and efficient display modality for functional imaging.

Proposed Course:

Cardiac Scintigraphy: LOGISK is a multiple group logistic discrimination program developed by Dr. Adlin Albert while a visiting scientist with LAS. This program will be used to find optimal combinations of parameters to separate normals from abnormals and focal from diffuse abnormalities. If successful, this methodology then can be applied to patients who develop congestive cardiomyopathy after therapy with adriamycin.

Tumor detection with monoclonal antibody dosimetry study: A small, known amount of Indium-tagged monocolonal antibody is injected intravenously. The amount and duration of uptake by the liver and spleen is calculated by integrating the counts in the manually delineated liver and spleen and comparing those counts to the counts in a scanned vial of a known amount of Indium. Studies will be directed toward liver and spleen dosimetry as this is the limiting dose in the use of the monoclonal antibodies for the detection of the metastatic spread of tumors such as mycoses fungoid and melanoma.

Gallium studies: Extensions of this work will require bronchial lavage data (i.e., quantity of inflammatory cells) in sets of cases in order to develop an accurate, objective, automated index without recourse to visual assessments. Further developments are deferred until the Pulmonary Branch reassigns someone to collaborate on this project.

Minicomputer and Desktop Usage: Increased use of the IBM PC XT for functional imaging and of the DeAnza imaging system is expected in the coming year for a study of paired myocardial (Thallium) and blood pool image sequences.

LAS members meet weekly with Nuclear Medicine staff to design a new computer-based system to replace the current nuclear medicine system. Design criteria include expandability, portability, ease of use, facilities for searches and sorts for the creation of data bases, and for archiving, which will include an online archive list, automated acquisition of data histories, and mechanisms to allow speed vs. space optimizations.

PET Scans and Biokinetics Studies: Investigators from NINCDS, NIMH, NIA, NHLBI, NCI, NIADDK, NICHD, and NIAAA have formed a task force with members of the Nuclear Medicine Department to embark upon a multitude of projects including studies of nerve cell metabolism and receptor function in such conditions as epilepsy, stroke, degenerative diseases (Alzheimers, ALS), neoplastic disease, and Korsakoff's psychosis; studies of ischemia in numerous cardiac conditions; and studies of antibody uptake in tumors. The Nuclear Medicine staff have requested that LAS assist in these studies, particularly in regard to evaluating data quality and appropriateness of models, (especially with simulations). Development of new models is anticipated. These activities could form the basis for a major effort by LAS in the coming years.

Publications and Abstracts:

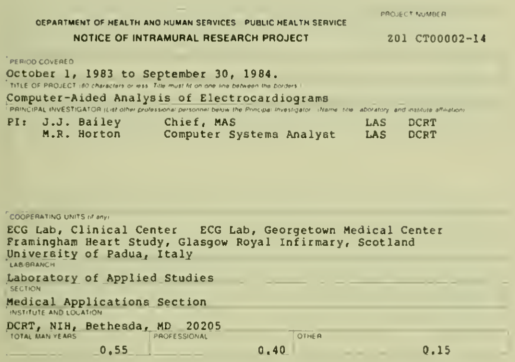
Bacharach, S.L., Green, M.V., Vitale, D., Bonow, R.O., Douglas, M.A., Jones, A.E., and Larson, S.M.: Fourier filtering cardiac time activity curves: Sharp cutoff filters. *8th International Conference on Information Processing-Medical Imaging* (in press).

Bacharach, S.L., Green, M.V., Vitale, D., White, G., Douglas, M.A., Bonow, R.O., and Jones A.E.; Optimum number of harmonics for filtering cardiac volume curves. *J. Nucl. Med.* 24:17, 1983.

Bailey, J.J., Douglas, M.A., Van Rijk, P.P., Green, M.V., Bacharach, S.L., and Bonow, R.O.: Parameters of regional wall abnormalities from radionuclide ventriculography. *Computers in Cardiology* (in press).

Van Rijk, P.P., and Bailey, J.J.: Nuclear cardiology. In van Rijk, P.P. (Ed.): *Nuclear Techniques in Medicine.* Den Haag, Nederland, Martinus-Nijhoff (in press).

Van Rijk, P.P. Bailey, J.J., Bacharach, S.L., Bonow, R.O., Green, M.V., and Palmeri, S.T.: Computerized methods for detecting regional wall motion abnormalities using radionuclide ventriculography. *European Heart Journal* (in press).



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00002-14

PERIOD COVERED
October 1, 1983 to September 30, 1984.

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Computer-Aided Analysis of Electrocardiograms

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.J. Bailey	Chief, MAS	LAS	DCRT
	M.R. Horton	Computer Systems Analyst	LAS	DCRT

COOPERATING UNITS (if any)
ECG Lab, Clinical Center ECG Lab, Georgetown Medical Center
Framingham Heart Study, Glasgow Royal Infirmary, Scotland
University of Padua, Italy

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.55	0.40	0.15

Computer-Aided Analysis of Electrocardiograms

These studies, continuing since 1970, are directed toward the evaluation of accuracy, clinical utility, and cost effectiveness of various computer programs for analysis of resting electrocardiograms (ECG's). Further studies will involve new methods of feature extraction and design of criteria by computer techniques and their use in epidemiological studies.

Progress During FY84: Analyses of the Framingham data have continued with LVH determined both by manual reading and by computer program (IBM). Of those with ECG criteria for LVH by manual reading, 80 percent have increased left ventricular mass by echo cardiographic examination and about 3 to 4 percent have LV mass at or about the upper normal limit. The remaining cases (about 16 percent) with ECG stigmata suggesting LVH, had normal LV masses by the Framingham criteria.

A comparison of manual readings with the IBM program shows about the same sensitivity to LVH; however, the IBM program is less specific than the manual readings. The IBM program relies heavily upon QRS voltage, whereas manual readings make more use of ST-T changes.

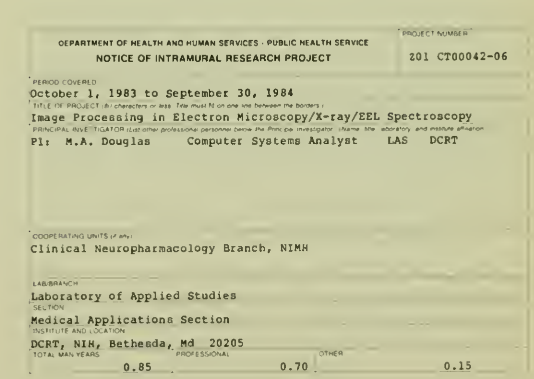
After nearly two years delay, Georgetown Medical Center has delivered digital data from 12 simultaneous lead ECG's. However, due to personnel shortages, LAS has not yet been able to format the data for analyses by other programs.

An ECG diagnostic program based upon fuzzy set theory, built by the Laboratory of Systems and Bioengineering (LADSEB), National Research Council of Italy, was tested with digital data from LAS. The theoretical advantage of fuzzy set theory should be that it lends stability to diagnostic statements in contrast to classical, discrete threshold, or decision tree methods now used by most programs. However, the LADSEB program showed a surprising variation when given two different digital representations of the same analog ECG.

Proposed Course: Analyses of the Framingham data will be summarized in a manuscript for publication. The appearance of ECG stigmata of LVH has prognostic significance for this population.

When time and personnel permit, the Georgetown data will be reformatted so that a comparison of several programs, including those of IBM, HP, GRI, and Duke University, can proceed.

The results of the reproducibility study suggest that the LADSEB program needs a major revision of its algorithms. Until this occurs, LAS will not pursue further studies with this program.



DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00042-06

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Image Processing in Electron Microscopy/X-ray/EEL Spectroscopy

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.A. Douglas	Computer Systems Analyst	LAS	DCRT

COOPERATING UNITS (if any)
Clinical Neuropharmacology Branch, NIMH

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Md 20205

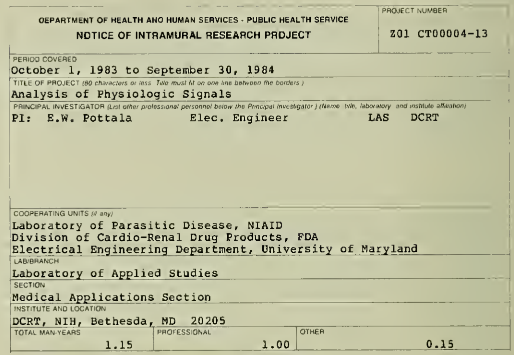
TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.85	0.70	0.15

Computer-based analysis and image processing in electron microscopy and x-ray and electron-loss spectroscopy

This project is directed toward the development of computer-based mathematical and statistical analyses, pattern recognition, and image processing of data, principally x-ray micrography and electron energy loss spectra, derived from the electron microscopy images of biological specimens.

Progress During FY84: A series of 512 x 512 pixel electron micrographs of dense bodies in human platelets before and after the addition of fluorine acquired at Brookhaven National Laboratories have been analyzed. The dense bodies were detected and delineated by two different operators, each using a semi-automated edge detection algorithm. Densities of each detected dense body have been computed. Statistical analyses have been performed on the data to determine the sample size necessary to detect reliably the changes in density of dense bodies in digitally-acquired, electron micrographs of platelets. A manuscript describing these results is being prepared.

Proposed Course: A detailed analysis using phantoms and specimens of known composition will commence in the coming year. This work is necessary in order to formulate appropriate mathematical/statistical models to investigate changes in the composition of platelets. At that time the signal to noise ratio in phantoms and biological specimens also will be examined. The effect of contamination and specimen destruction by the high energy electron beam will be investigated. Efforts will continue in the development of algorithms for image enhancement and for automated element recognition and delineation.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00004-13

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Analysis of Physiologic Signals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: E.W. Pottala Elec. Engineer LAS DCRT

COOPERATING UNITS *(if any)*
Laboratory of Parasitic Disease, NIAID
Division of Cardio-Renal Drug Products, FDA
Electrical Engineering Department, University of Maryland

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.15	1.00	0.15

Analysis of Physiologic Signals

This project uses minicomputer techniques to analyze physiologic signals such as electrocardiograms, electroencephalograms, and electromyograms.

Progress During FY84: FDA has studied cardiogenic effects of a high lipid diet on 30 rats. Over 300 ECG's on these animals have been processed and the results are currently under review by the collaborating FDA pharmacologist prior to manuscript development.

The methods for processing the rodent ECG data acquired by the FDA are being published as a master's thesis (Electrical Engineering Department, University of Maryland) and in a biomedical journal.

NIAID is studying cardiac pathology in mice infected with Trypanosomi Cruzi (Chagas' disease). At midstudy over 900 ECG's on 420 mice have been processed by LAS systems for ECG analysis.

Proposed Course: The FDA anticipates additional rat studies involving cardiotoxicity of drugs, fad diets, and/or food additives.

The mouse data will require some reprogramming of the published methods since the NIAID cart differs from the FDA cart in format for leads, and also, since the mouse ECG differs from the rat ECG in some signal features.

The use of the MAC-16 system for ECG processing for the Framingham Heart Study (see project report on electrocardiography), as well as for processing the rodent ECG's, is continuing.

Publications:

Le, H. T., Van Arsdel, W. C., Makowski, A., Pottala, E. W., and Bailey, J. J.: Automated analysis of rodent electro-and vectorcardiograms. *IEEE Biomed. Trans.* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00005-14

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Mathematical Models of Binding Equilibria

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: J.E. Fletcher Chief, Applied Mathematics Sect. LAS DCRT

COOPERATING UNITS (if any)
Medical College of Georgia, VA Medical Center

LAB BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.15	0.10	0.05

Mathematical Models of Binding Equilibria

The objective of this project is the study of mathematical models of ligand-receptor or ligand-macromolecule binding studies at equilibrium. The models are examined for mathematical as well as for conceptual validity, and the models are explored parametrically to determine their suitability for fitting to experimentally obtained laboratory data. The appropriateness of various model fitting criteria are studied and general guidelines and computational algorithms are designed for computer-aided interactive model fitting.

Progress in FY84: No new analytical models were examined in FY83, although a number of literature critiques were requested by *Science* magazine. Requests for copies of exportable computer algorithms continued to be filled and a number of brief Institute consultations were provided. A summary report including collected results from 15 years of research in this area continues to be distributed and cited. The principal investigator continues to serve as a consultant, lecturer, and literature reviewer in this area. Detailed consultations and advice were provided to an investigator at the Medical College of Georgia.

Proposed Course: Consultations on new methodology and data analysis will continue to be made as they are requested by collaborating laboratories. Analytical development of new models and continued research in fitting methodology in this area will emphasize validation of experimental techniques, multi-receptor models, multi-ligand systems, and other special systems as required by collaborating investigators.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00044-06

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Mathematical Modeling of Substate Transport

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: J.E. Fletcher Chief, Applied Mathematics Sect. LAS DCRT

COOPERATING UNITS (if any)
Dept. of Biomedical Engineering, LTU

LAB BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.45	0.35	0.10

Mathematical Modeling of Substate Transport in Physiological Environments

Mathematical models of microcirculatory structure and function are developed from conceptual models into systems of coupled ordinary and/or partial differential equations. Methods of solution of these nonclassical formulations are developed and tested, and satisfactory cost effective methods are used to explore the properties of these models. The model simulations are interpreted in terms of microcirculatory physiology.

One objective of this project is to study whole organ response and organ tissue level phenomena by means of mathematical models in an effort to determine relationships between variables that govern the organ response to physiologic challenges.

Progress in FY84: Investigations were completed for the modeling and analysis of red cell-free perfused organ experiments. The new model was found to be more satisfactory for compatibility with the experimental design. This model included capillary diffusion effects and examined the effects of a varying capillary wall permeability. Manuscripts describing a number of parametric studies with this model have been published and an extensive manuscript summarizing the results has been submitted.

Additional investigations of models of red cell oxygen unloading have been carried out and the results indicate that a number of controlling factors may be involved. The question of resistance to oxygen transport from intra-red cell oxyhemoglobin to cell mitochondria appears to require considerable re-examination. Experiments currently are underway elsewhere to suggest what features need to be amplified.

Proposed Course: Research into both of the above areas will continue in FY85, but at a much reduced level because of intense administrative demands on the principal investigator's time. Further modeling studies with the heart data may involve the role of myoglobin in preferential axial transport, as well as an examination of spatial and temporal heterogeneities.

Publications:

Fletcher, J.E.: Some mathematical questions arising from modeling of the microcirculation. SMU Math Series, Dallas, Texas, 1983.

Fletcher, J.E., and Schubert, R.W.: Capillary wall permeability effects in capillary-tissue structures. In Bruley, D., Horton, C., and Buerk, D. (Eds.): *Oxygen Transport to Tissue-VI.* New York, Plenum Press (in press).

Fletcher, J.E., and Schubert, R.W.: Diffusional coupling in a hemoglobin-free perfused capillary-tissue structure. In Lubbers, D. Acker, H., Leniger-Folert, E., and Goldstick, T. (Eds.): *Oxygen Transport to Tissue-V.* New York, Plenum Press, 1984, pp. 145-160.

Fletcher, J.E., and Schubert, R.W.: The theoretical prediction of substrate levels and their histograms in cell free perfused tissues. In Bicher, H., and Bruley, D. (Eds.): *Oxygen Transport to Tissue-IV.* New York, Plenum Press, 1983, pp. 599-612.

Fletcher, J.E., Schubert, R.W., and Reneau, D.D.: An analytical model for axial diffusion in the Krogh cylinder. In Bruley, D., Horton, C., and Buerk, D., (Eds.): *Oxygen Transport to Tissue-VI.* New York, Plenum Press (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT		PROJECT NUMBER Z01 CT00112-02
PERIOD COVERED October 1, 1983 to September 30, 1984		
TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Network Modeling in Biology		
PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)* PI: B. Bunow Expert LAS DCRT E.W. Pottala Engineer LAS DCRT		
COOPERATING UNITS *(if any)* Medical College of Virginia; NIOSH, Blacksburg, Va.; LMB, NIADDK; LSM, DCRT; LNC, NINCDS		
LAB/BRANCH Laboratory of Applied Studies		
SECTION		
INSTITUTE AND LOCATION DCRT, NIH, Bethesda, Md. 20205		
TOTAL MAN-YEARS 0.55	PROFESSIONAL 0.40	OTHER 0.15

Network Modeling in Biology

This project has two parts: 1. evaluation, application, and support of network modeling languages for the description and simulation of complex biological models, and 2. the design, implementation, and documentation of a new network modeling language. Simulation, computer programming, and formal language processing are the main tools in these investigations.

- Network Modeling in Biology with Existing Network Languages

Background and Objectives: Mathematical modeling in biology is especially difficult because of the need to be familiar with both the biological basis of the problems and the mathematical tools required for their solution. Network modeling, supplemented with effective languages for describing the models on computers, largely obviates the need for extensive mathematical sophistication, and makes the process of model formation and testing accessible to biologists lacking such skills. Topological modeling is particularly appropriate to biological problems because the objects of study generally satisfy essentially topological conservation laws. In biological systems, the processes of flow, accumulation, and chemical transformation are fundamental; these are likewise the basic operations in network modeling.

Significance for Biomedical Research: The choice of a model for a biological process strongly conditions the design of experiments to confirm and test it. By making the analysis of models sufficiently simple, flexible, and powerful, we permit an investigator to consider alternative models, including those which include his fullest conceptualization of the biological phenomena. For example, in neuronal modeling, an anatomically-based model for the entire dendritic field of a CNS neuron has been constructed and validated by comparison to experimental measurement. The computer representation could then be subject to new "experiments" providing the basis for a more complete understanding of neuronal functioning and for further experimental investigation.

Progress During FY84: The latest versions of NET-2 and SPICE have been installed both at NIH and FDA.

The respirator model developed in FY83 in collaboration with NIOSH has been completed and presented at a OSHA New York Meeting, March, 1984.

An anatomically-based model of the dendritic field of a CNS neuron has been developed in collaboration with LNC/NINCDS. Subthreshold voltage levels and AC impedance and transfer characteristics have been measured in the model and shown to match nicely to experimental data. This research has been presented at the Society for Neurophysiology, March, 1984 and a manuscript has been accepted for publication.

A computationally efficient representation of an active (Hodgkin-Huxley) neuronal membrane has been developed and validated.

Future Course: Several NIH laboratories at NINCDS and NIADDK now use network modeling extensively and this project will continue to collaborate and provide consulting assistance. In particular, SPICE models for electrically active ionic channels in nerve membranes will be developed and tested.

A major problem for application of SPICE to biological problems is the cost of computer time on the central facility. For this reason, we propose to port SPICE onto an IBM PC XT. While this combination is too slow for studying very large models, it may be effective for submodel development as well as for studying systems of modest size. Adequate software support for this portation just now has become available from vendors.

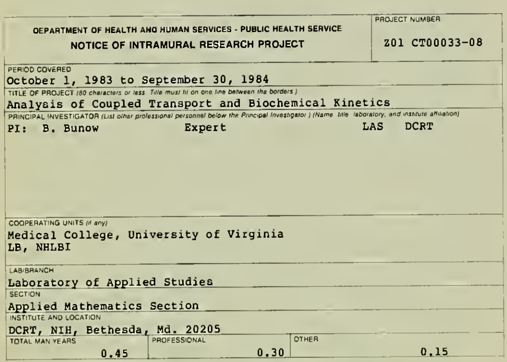
- A New Network Modeling Language

Background and Objectives: The weaknesses of current network languages have encouraged the development of a new network language intended to be particularly appropriate to biological modeling. This language will be named ALEMBIC, an acronym for A Language for Expressing Models in Biology In Computers. The mathematical approach of the language is a nonlinear generalization of compartmental analysis, while the implementation is through a macrotranslator that produces MLAB programs as output.

Significance for Biomedical Research: Creation of complex models is much easier in ALEMBIC than in MLAB. The usual progression in modeling is from an analytical model that can be analyzed on paper to a more complex model that is to be analyzed with MLAB, and finally to a model that is too complex to be conveniently expressed in MLAB. While this final class of models is too complex to be used for data fitting, it provides a workbench on which to test the validity of simplifications from reality, which are ordinarily unexamined because to do so would be too time-consuming.

Progress During FY84: This project has been put on hold pending settlement of the issue of support for such a long-term project.

Future Course: The completion of the ALEMBIC translator is a major project whose completion will be a matter of several years. However, in FY85 considerable progress should be achieved. The user's manual will be extended to include not only specification of the syntax, but also a compendium of relatively elaborate examples that call upon the full power of the language.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00033-08

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Analysis of Coupled Transport and Biochemical Kinetics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: B. Bunow Expert LAS DCRT

COOPERATING UNITS (if any)
Medical College, University of Virginia
LB, NHLBI

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Md. 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.45	0.30	0.15

Analysis of Coupled Transport and Biochemical Kinetics

This project investigates two fundamental problems in biology: the kinetics of enzymes located in cell membranes, and the thermodynamics of bioenergetic mechanisms in mitochondria. Mathematical analysis, simulation on digital computers, and numerical solution of nonlinear algebraic and differential equations are the main tools in these investigations. While these problems are diverse in their biological background, they all share in a common basis of mathematical and physical content in the role played by conservation laws and in the mathematical methods involved in their resolution.

- The Kinetics of Enzymes in Membranes

Background and Objectives: Studies of the mechanism of membrane transport and energy transduction by enzymes in membranes are generally less conclusive than studies of the mechanisms of isolated enzymes. This uncertainty arises because it is difficult both to manipulate the environment of the interior of a biological membrane and to measure responses there. The objective of this project is to determine the extent to which the actual organization of membrane-associated, enzyme-catalyzed processes can be correctly inferred from the application of models, either detailed or phenomenological, to the kinds of experimental measurements currently made.

Significance for Biomedical Research: Studies of membrane-associated enzymes, such as those of mitochondria, for example, are made by measuring external concentration changes, from which one attempts to infer the biochemical mechanism. This process is evidently unreliable, as witnessed by a decades-long controversy over almost every detail of the mechanism. A consequence of our work is to suggest strongly that this lack of reliability is intrinsic. It is a result of incompatibility between the essentially macroscopic nature of the experimental observations, on the one hand, and the molecular character of the questions that are posed, on the other hand. For this reason, the problem is not to be resolved by performing yet another experiment of the kinds currently popular, no matter how ingenious.

Progress During FY84: One widely used alternative to the approach described above is to seek a phenomenological description of these systems using classical nonequilibrium thermodynamics. The two fundamental premises of this technique, termed linearity and reciprocity, have been shown to lack generality, and, indeed, to be specifically inapplicable to systems in which chemical reactions are important.

The manuscript describing experimental work in this area will be published shortly. A second manuscript detailing the inadequacy of nonequilibrium thermodynamics for characterizing this class of biological systems is under review.

Future Course: The goal for FY85 will be to examine the incremental response of nonlinear reaction-diffusion systems that are maintained in a far-from-equilibrium stationary state. Because the important examples are all nonlinear, numerical rather than analytical methods will be needed.

- Thermodynamics of Bioenergetic Systems

Background and Objectives: The mechanism by which the generally reduced components of nutrients are oxidized in mitochondria is still elusive, although most of the components of this pathway have been identified. The membrane association of the components makes it difficult to proceed in the usual biochemical manner of molecular dissection and reconstitution. Most experimental studies are made on systems that are quite structurally complex. Nevertheless, interest focuses on the usual biochemical question: What is the sequence of molecular forms involved in the bioenergetic pathway? The role of the electron donor, ubiquinone, in this pathway is the particular object of our interest in this project.

Significance for Biomedical Research: An understanding of the mechanism of the central energy-yielding process of living organisms is clearly essential. Thermodynamic analysis has shown that the accepted explanation for the phenomenon of oxidant-induced reduction of cytochrome b in the presence of antimycin cannot be correct. Presentation of a sound physical basis for analyzing multielectron transfer reaction will assist many groups working on this problem who have previously accepted an invalid argument.

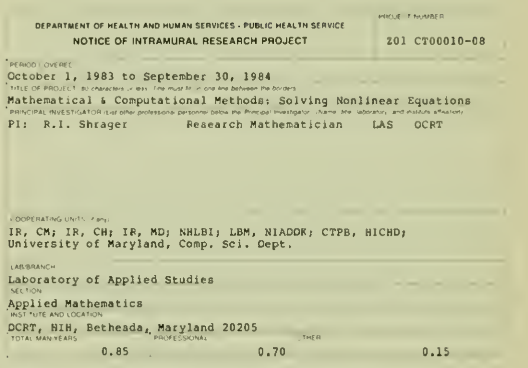
Progress During FY84: The manuscript describing this work has been accepted. Continuing collaboration between LAS and Dr. Hendler has included consultation on electrochemistry, thermodynamics, and biophysical principles involved in bioenergetic systems.

Future Course: In addition to the Q-cycle, there are numerous examples of electrochemical processes in bioenergetics. Their critical analysis will be the subject of our attention in the coming year.

Publications:

Bunow, B.: Determination of the distribution of catalyst activity across a permeable membrane containing an immobilized enzyme. Indeterminacy of a functional approach to a structural problem. *Biophys. J.* 45: 1065-1071, 1984.

Hendler, R.W., Bunow, B., and Rieske, J.: Thermodynamic and Kinetic Considerations of Q-cycle Mechanisms. *Rev. in Bioenergetics* (in press).



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
201 CT00010-08

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Mathematical & Computational Methods: Solving Nonlinear Equations

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: R.I. Shrager Research Mathematician LAS OCRT

COOPERATING UNITS (if any)
IR, CM; IR, CH; IR, MD; NHLBI; LBM, NIADDK; CTPB, NICHD;
University of Maryland, Comp. Sci. Dept.

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS: 0.85
PROFESSIONAL: 0.70
OTHER: 0.15

Mathematical and Computational Methods for Solving Nonlinear Equations

Methods are developed for solving nonlinear equations frequently encountered at NIH. These equations are usually encountered in the context of constrained nonlinear least squares problems or in the numerical solution of nonlinear differential equations. Related problems, such as asymptotic error analysis and the efficient treatment of sparse matrix systems, also are considered.

Progress During FY84: A second revised manuscript of "A rapid, robust rootfinder" has been accepted by a journal. The function minimizer developed by visiting fellow Dr. Behrooz Kamgar-Parsi is being extended to handle linear constraints on the parameters. A computer program for solving systems of differential-algebraic equations currently is being tested. Some components of MLAB, a mathematical-graphics package, are being examined for individual use on an IBM PC. A study of new forms of computer arithmetic was undertaken in order to anticipate the merits and pitfalls of the personal computer coprocessors and the IBM ACRITH package.

Circular dichroism (CD) spectra, as processed by a singular value decomposition (SVD) method developed here, are being used to probe the effect of calcium, magnesium, and manganese on calmodulin, an important neurological control enzyme. Work was delayed on this for lack of sufficient calmodulin, but new production techniques have allowed us to resume. SVD treatment also is planned for protein folding studies using CD data from Dr. McPhie (NIADDK). Actual experiments await arrival of some of Dr. McPhie's computer hardware.

A program developed at LAS, written in the formal language REDUCE, produces exact coefficients of digital filters. These filters have been applied in Dr. Hendler's laboratory (NHLBI) to correct for electrode delays and currently are being applied to 252-Californium-Plasma desorption mass spectrometry in Dr. Fales lab (NHLBI). A computational method for deducing voltage from current in a coulometric experiment currently is being developed for Dr. Hendler's experiments on cytochromes in cell membranes.

Dr. Munson (NICHD) is applying a curve-fitting technique known as L-one, developed in part at LAS to resolve equilibrium constants in double-ligand binding experiments.

Proposed Course: The Calmodulin experiment should proceed smoothly barring further hardware difficulties and the protein folding studies should begin in earnest. Mass spectrometry processing should become routine following a specification of the frequencies to be passed by the filter or filters. Coulometric experiments will begin this year. Dr. Kamgar will extend his work on a multivariate root finder. Work on the differential-algebriac system solver and on a PC-based modeling system will continue as time permits. Finally, this year has seen a signigicant increase in outside consultations on a short-term basis. This trend is expected to increase sharply with the arrival of more stand-alone or personal computers.

Publications and Presentations:

Ferenci, P., Covell, D., Schafer, D.F., Waggoner, J.G., Shrager, R., Berman, M., and Jones, A.E.: Metabolism of the inhibitory neurotransmitter alpha-amino-butyric acid in a rabbit model of fulminant hepatic failure. *Hepatology* 3(4): 507-512, 1983.

Hendler, R.W., Setty, O.H., Shrager, R.I., Songco, D.C., and Friauf, W.S.: Instrumentation and procedures for real time measurements of proton motive force, membrane potential, delta pH, proton extrusion, and oxygen uptake in respiring cells and vesicles. *Rev. Sci. Instrum.* 54(12): 1749-1755, 1983.

Setty O.H., Hendler, R.W., and Shrager, R.I.: Simultaneous measurements of proton motive force, delta pH, membrane potential, and H/O ratios in intact Escherichia Coli. *Biophys. J.* 43: 371-381, 1983.

Shrager, R.I.: A rapid robust rootfinder. *Mathematics of Computation* (in press).

Shrager, R.I.: A rapid robust rootfinder. SIAM Fall Meeting, Norfolk, Virginia, 1983.

Shrager, R.I.: Optical spectra from chemical titration, An analysis by SVD. *SIAM J.* Algebraic Discrete Methods (in press).

Shrager, R.I.: Some pitfalls in the use of derivative spectra. *Photochem. Photobiol.* 38(5): 615-617, 1983.

Winslow, R.M., Samaja, M., Winslow, N.J., Rossi-Bernardi, L., and Shrager, R.I.: Simulation of continuous blood O2 equilibrium curve over physiological PH, DPG, and PCO2 range. *J. Appl. Physiol. (Resp., Envir., & Exercise Physiol.)* 54(2), 1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00045-06

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
The Solution of Reaction-Diffusion Systems in Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M. Bieterman	Staff Fellow	LAS DCRT
	J.E. Fletcher	Research Mathematician	LAS DCRT
	I. Babuska	IPST and Dept. of Math.	Univ. of MD
	D. Covell		LMB NCI

COOPERATING UNITS (if any)

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Applied Mathematics Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.95	1.80	0.15

The Solution of Reaction-Diffusion Systems in Biology

This project consists of the development of numerical methods and mathematical software for the solution of partial differential equations describing dynamic physiological processes. Adaptive finite element techniques have been generalized and used for models of nerve conduction, oxygen transport in tissue, uptake of macromolecules into the lymphatic system, and in preliminary studies of subsurface contaminant flow. FORTRAN coded packages implementing these and other techniques are available for use on the major DCRT computers.

Progress During FY84: The focus of this project has been the further development and application of numerical methods--particularly adaptive finite element methods--for the solution of partial differential equation models of dynamic reaction-diffusion processes in one space dimension. The adaptive methods are implemented in the FORTRAN package FEMOL1. Other related activities have included: the collection of many recently developed scientific subroutine packages for use in mathematical modeling of biological systems; modeling and software assistance given to NIH researchers; preliminary progress made in the study of approximation methods for subsurface contaminant transport problems; and initial investigations made of software for differential/algebraic equations arising, for example, in modeling coupled chemical reactions proceding at greatly disparate rates.

Adaptive finite element methods, which feature automatic adjustment of space and time discretizations, have been studied over the past several years in LAS. Several improvements in the software implementing these techniques were made during FY84. FEMOL1 now has capabilities to solve problems in which the diffusive and convective transport terms and boundary conditions depend nonlinearly on solution components. The program has been restructured so that it is accessible at three levels: by a casual user, by one wishing to control many of the program's internal numerical parameters, and by one studying or wishing to override the automatic decisions that are made. Applications of FEMOL1 have been made to models of substrate transport, nerve conduction, mobile populations in ecosystems, and simple flows in porous media.

Many state-of-the-art mathematical subroutine packages have been obtained and tested by the LAS staff. These routines provide capabilities to directly and iteratively solve sparse matrix equations arising in large-scale scientific computations, to solve dynamic partial differential equations with unchanging space grids in two space dimensions, to solve stiff and nonstiff implicit systems of ordinary differential and differential/algebraic equations, and to solve steady state partial differential equations with adaptive discretizations in two space dimensions.

These subroutines increase the modeling support that can be given to NIH researchers and aid new software development in DCRT. In FY84, for example, assistance was given to D. Covell of NCI, LMB with partial differential equation routines in a design of models of macromolecule uptake into the lymphatic system. These efforts are directed toward the use of monoclonal antibodies to diagnose and treat cancerous tissue. Experience with the sparse matrix routines aided assistance given to R. Chadwick of DRS, BEIB this past year. A feasibility study was made of a three-dimensional computational fluid flow model to examine the effects of tortuosity of blood vessels located, for example, in contracting heart muscle. With R. Shrager of DCRT/LAS, differential/algebraic equation software was examined in FY84. These efforts are directed toward adding such capabilities to MLAB, or an MLAB-like system in the future.

Much of the new software mentioned above was obtained by the principal investigator while on assignment as a research associate in the Computer Science Department of Yale University. Background investigations were conducted there of "splitting" numerical methods appropriate for models of contaminant transport in porous subsurface media. Such flows often are highly convective, and splitting methods can resolve convective and diffusive transport terms independently in a stable manner. Investigation of splitting methods was curtailed in FY84, due to other priorities and a lack of expected modeling support from NIEHS scientists, but partial findings have aided other modeling and software development.

Proposed Course: This project will expand in the directions described above and branch into new areas. The focus of new activity will be the development of adaptive finite element methods for dynamic models in two space dimensions. Objectives leading to a finished software package include analysis and implementation of discretization error estimators, extension of the multigrid spatial pattern recognition processes used in FEMOL1, incorporation of an appropriate data structure and sparse matrix package, and design of a user interface. These goals cannot possibly all be achieved in FY85, but work towards them will directly benefit other concurrent project efforts, just as the development of adaptive methods in one space dimension has done in the past.

Publications and Abstracts:

Bieterman, M.B.: Accuracy estimation and control in a method for diffusion-dominated transport problems. *Proc. of the First Internat. Conf. on Accuracy Estimates and Adaptive Refinements in Finite Element Computations (ARFEC).* Lisbon, Portugal, 1984, pp. 107-118.

Bieterman, M.B.: A posteriori error estimation and adaptive finite element grids for parabolic equations. In Babuska, I., Chandra, J., and Flaherty, J.E. (Eds.): *Adaptive Computational Methods for Partial Differential Equations.* SIAM Publications, Philadelphia, 1983, pp. 123-143.

Bieterman, M.B.: On using local solution information in regridding for time-dependent equations. NASA-ICASE Workshop on Grid Methods, Hampton, Virginia, 1983.

Bieterman, M.B. and Babuska, I.: An adaptive method of lines with error control for nonlinear parabolic equations of the reaction-diffusion type. *J. of Computational Physics* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00121-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Personal Computers in the NIH Research Environment

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	M.R. Horton	Computer System Analyst	LAS	DCRT
	R.C. Burgess	Senior Staff Fellow	LAS	DCRT
	M.A. Douglas	Computer Systems Analyst	LAS	DCRT
	E.W. Pottala	Electronics Engineer	LAS	DCRT
	B.J. Bunow	Expert	LAS	DCRT
	R.I. Shrager	Research Mathematician	LAS	DCRT
	H.T. Le	Electronica Engineer	LAS	DCRT

COOPERATING UNITS (if any)
Personal Workstation Project DCRT

LAB/BRANCH
Laboratory of Applied Studies

SECTION
Medical Applications Section

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, MD 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.65	0.55	0.10

Personal Computers in the NIH Research Environment

In this project, a variety of personal computer-based systems is assembled and investigated for the ability to adapt various kinds of research projects to them. In general, research projects often require such activities as laboratory data acquisition and analysis, physiological imaging, mathematical modeling, and numerical analysis. Commercially available hardware and software components of microcomputer systems purport to be highly advantageous in such research systems and need critical examination and evaluation to determine their true capabilities and appropriate use. This examination is the objective of this project.

This project is designed to determine appropriate uses for personal computers in the research laboratory, and to develop prototype personal-computer-based systems to achieve research objectives including laboratory data acquisition, analysis, and display.

Background and Objectives: The development of personal microcomputers, which has been underway by commercial computer vendors for the past several years, has arrived at the stage where it is feasible to utilize a personal computer as a powerful tool in laboratory research as well as an aid to management. Because the technological advances in microcomputer architecture are occurring so rapidly, the peripheral equipment and software needed for laboratory applications are appearing on the market in explosive fashion. The evaluation and selection of available, useful equipment and software, and the development of microcomputer-based laboratory systems are the objectives of this project.

Significance of Biomedical Research: Microcomputer-based laboratory systems, if configured with appropriate peripheral data acquisition and display equipment and software can bring into the hands of biomedical researchers the power of computing tools. Discovery of the appropriate balance of mainframe and personal computing will lead to increased utilization of powerful research tools while helping to hold down costs of research.

Progress During FY84: In collaboration with the Personal Workstation Office (formerly, Personal Workstation Project), DCRT, hardware has been acquired to configure three different personal-computer-based systems: one is particularly suited for image processing and graphics displays; one is for laboratory data acquisition and analysis; and one for mathematical modeling and large-scale numerical analysis. A number of software packages have been acquired and tested on the three systems. An intensive investigation and evaluation has been carried out on many of these hardware and software components. These include:

color/graphics boards
realtime data acquisition boards
hard disk drives
the Intel 8087 arithmetic coprocessor
color monitors
C-language compilers

FORTRAN language compilers
graphics software packages
word processing packages
data base management packages

Written evaluations of the tested products have been provided to the Personal Workstation Office.

Future Course: Evaluation of hardware and software products will continue, especially as new products become available. Intensive efforts will be made in two areas:

1. Development of a true imaging system, capable of competing favorably with much more expensive minicomputer-based systems. The expectation is that appropriate hardware will be available within the year and efforts will be directed toward providing effective input, processing, and display techniques for analyzing research data.
2. Determining whether or not the readily available IBM PC XT's can serve as inexpensive but effective laboratory data-acquisition controllers.

Demonstration of the applicability of personal-computer-based systems in biomedical research will be undertaken in connection with ongoing LAS projects, including computer systems for nuclear medicine and for the analysis of physiologic signals.

Dr. V. Adrian Parsegian studies molecular forces in cellular assembly. Direct measurement of forces between DNA helices has determined that hydration forces play a considerable role in the interaction of molecular surfaces.

Physical Sciences Laboratory

George H. Weiss, Chief

Summary of Activities

Consulting Services. George H. Weiss (PSL). Consulting services are offered by members of the PSL to other researchers at NIH in selected areas in chemistry, physics, and applied mathematics.

Molecular Forces in Cellular Assembly. Adrian Parsegian (PSL). The goal of this project is to identify and measure forces important in cellular assembly. Direct measurement of forces between DNA helices has determined that hydration forces play a considerable role in the interaction of molecular surfaces and may override forces earlier conjectured to be the most important ones in such systems.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph Nossal (PSL). In this project, light scattering techniques are used to measure physical properties of materials of biological interest. New methods have been devised for analyzing light scattering measurements of gelation properties and elasticity of polymer networks.

Membrane Transport and Fusion. Joshua Zimmerberg (PSL). Measurements have been made of volume changes that occur with channel opening and closings, for voltage-dependent ionic channels in membranes. These measurements are the first ever made of volume changes of such channels, and clearly indicate that currently accepted models of membrane transport are incorrect.

Biophysical Analysis. Ralph Nossal (PSL). Studies have been initiated on the development of models suitable to describe dense macromolecular systems. Models that involve fractals and percolation theory have been used for this purpose.

Effect of Solvent on Biological Macromolecules. B. K. Lee (PSL). Statistical mechanical methods have been used to study the hydrophobic behavior of macromolecules as influenced by solvents. The theory has been developed for spherical molecules so far and a start has been made on developing a similar theory for nonspherical molecules.

Studies in Mathematics and Statistics. George Weiss (PSL). Mathematical and computer methods have been used to study diffusion in a field of reaction centers or traps, to establish the kinetics of such systems. Results of the study indicate that the mathematical theory of such systems is valid only when an unrealistically large degree of reaction has occurred.

Instrumental Analysis. George Weiss (PSL). Exact solutions have been provided for models used in the analysis of crystallographic data. These solutions are generally easy to compute and replace approximate results that can be quite inaccurate in the presence of atomic heterogeneity.

Correlation Function Spectroscopy/Laser Light Scattering. Ralph Nossal (PSL). Techniques for the analysis of gelation and elastic properties of polymer lattices by dynamic light scattering measurements have been developed. These techniques allow estimation of the relation between monomer concentrations and the cross-link density necessary for gelation to occur.

Computerized Typesetting of Scientific Papers. Nancy Crawford (PSL). Experiments have been conducted on optimal distribution of the different efforts required for typesetting between microprocessors and mainframe computers.

Personal Workstation Project--Word Processing Subproject. Nancy Crawford (PSL). Eleven word processor software packages have been evaluated for use on the IBM PC. Using criteria that have been set by workers in the subproject, one such package has been selected as the best to date.

Research Projects

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00014-17

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Instrumental Analysis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	George H. Weiss, Ph.D.	Chief	PSL	DCRT
	J. E. Kiefer		PSL	DCRT
	U. Shmueli, Ph.D.		Tel-Aviv Univ., Israel	
	A. J. C. Wilson		Cambridge Univ., London	

COOPERATING UNITS (if any)

LAB/BRANCH
Physical Sciences Laboratory

SECTION

INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.4	0.3	0.1

Instrumental Analysis

Mathematical techniques are developed and applied to the analysis of data processing methods and the design of experiments to maximize precision of estimated parameters. Exact representations have been obtained for the probability densities of random walk models that are used in crystallography. These are now available for a large number of space groups as well as for noncrystallographic symmetries.

Publications:

Shmueli, U., Weiss, G. H., Kiefer, J. E., and Wilson, A.J.C.: Exact random walk models in crystallographic statistics. I. Space groups P1 and P1. *Acta Crystallographica* (in press).

Weiss, G. H., and Kiefer, J. E.: On the probability density of the envelope of a sum of random vectors. *J. Sound and Vib.* (in press).

Weiss, G. H., and Kiefer, J. E.: Random walks in crystallography. *Persp. in Stat. Mech.* (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 CT00022-17

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Consulting Services

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	George H. Weiss, Ph.D.	PSL	DCRT
	J. E. Kiefer	PSL	DCRT
	R. J. Nossal, Ph.D.	PSL	DCRT
	R. A. Brooks	SN	NINCDS
	J. A. Ferretti	IR CH	NHLBI
	R. Carson	NM	CC

COOPERATING UNITS (if any)

LAB/BRANCH
Physical Sciences Laboratory

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INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.8	0.5	0.3

Consulting Services

Members of the PSL provide consulting services in the physical sciences and applied mathematics to researchers at NIH. Current examples of such consulting include optimization of NMR experiments and biological tracer experiments. Some present problems include the optimization of experiments designed to measure the spin-lattice relaxation time in chemical applications of NMR. Other problems of interest include techniques for reducing two-dimensional NMR data as well as the principles of experimental design in NMR imaging. Similar techniques are currently being applied to the kinetics of biological tracer experiments such as are used in PET scanning and diagnostic technologies currently under development.

Publications:

Rish, B. L., Dillon, J. D., and Weiss, G. H.: Mortality following penetrating craniocerebral injuries. An analysis of deaths in the Vietnam Head Injury Registry population. *J. Neurosurg.* 59: 775-780, 1983.

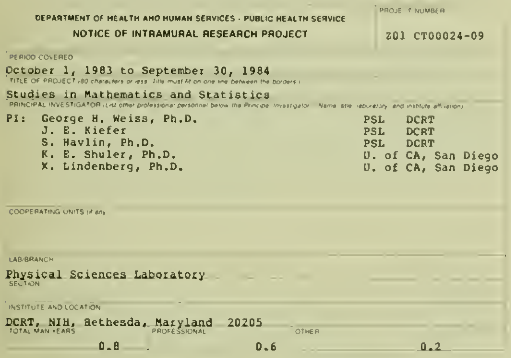
Stone, M., Sonies, B. C., Shawker, T. H., Weiss, G. H., and Nadel, L.: Analysis of real-time ultrasound images of tongue configuration using a grid-digitizing system. *J. Phonetics.* 11: 207-218, 1983.

Weiss, G. H., and Aron, J. L.: Note on the formulation of a stochastic model of super-infection. *Math. Biosc.* 67: 213-223, 1983.

Weiss, G. H., and Ferretti, J. A.: Accuracy and precision in the estimation of peak areas and NOE factors. *J. Mag. Res.* 55: 397-407, 1983.

Weiss, G. H., Ferretti, J. A., Kiefer, J. E., and Jacobson, L.: A method for eliminating errors due to phase imperfection in NOE measurements. *J. Mag. Res.* 53: 7-13, 1983.

Weiss, G. H., and Szabo, A.: First passage time problems for a class of master equations with separable kernels. *Physica* 119A: 569-579, 1983.



PROJECT NUMBER

Z01 CT00024-09

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Studies in Mathematics and Statistics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	George H. Weiss, Ph.D.	PSL DCRT
	J. E. Kiefer	PSL DCRT
	S. Havlin, Ph.D.	PSL DCRT
	K. E. Shuler, Ph.D.	U. of CA, San Diego
	K. Lindenberg, Ph.D.	U. of CA, San Diego

COOPERATING UNITS (if any)

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TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.8	0.6	0.2

Studies in Mathematics and Statistics

Considerable effort was devoted to the study of the trapping of random walks. These are important as models of energy transfer in molecules. Numerical techniques have been developed for calculating survival probabilities and other parameters that characterize diffusive motion of a random walk in a field of traps. This theory has applications to the kinetics of chemical reactions in solution.

Publications:

Havlin, S., Weiss, G. H., Kiefer, J. E., and Dishon, M.: Exact enumeration of random walks with traps. *J. Phys.* A17: L347-350, 1984.

Kiefer, J. E., and Weiss, G. H.: The Pearson random walk. AIP Proceedings 109: 11-32, 1984.

Otterman, J., and Weiss, G.H.: Reflection from a field of randomly located vertical protrusions. *Appl. Opt.* (in press).

Szabo, A., Lamm, G., and Weiss, G. H.: Localized partial traps in diffusion processes and random walks. *J. Stat. Phys.* 34: 225-238, 1984.

Weiss, G. H.: A perturbation analysis of the Wilemski-Fixman approximation for diffusion-controlled reactions. *J. Chem. Phys.* 80: 2880-2887, 1984.

Weiss, G. H.: First passage times for correlated random walks and some generalizations. *J. Stat. Phys.* (in press).

Weiss, G. H.: Passage times. *Ency. Stat. Sci.* (in press).

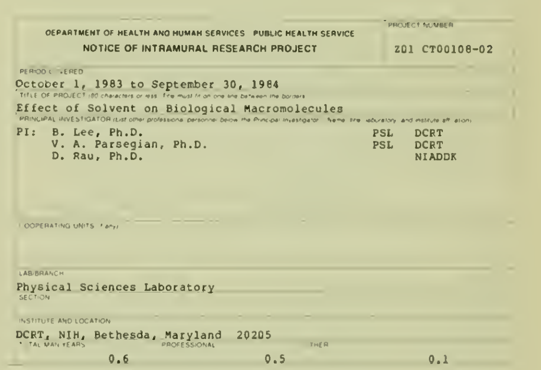
Weiss, G. H.: Random walks. *Ency. Stat. Sci.* (in press).

Weiss, G. H.: Saddle-point approximations. *Ency. Stat. Sci.* (in press).

Weiss, G. H.: Tauberian theorems. *Ency. Stat. Sci.* (in press).

Weiss, G. H.: Wald's identity. *Ency. Stat. Sci.* (in press).

Weiss, G. H., and Havlin, S.: Trapping of random walks on the line. *J. Stat. Phys.* (in press).



PROJECT NUMBER

Z01 CT00108-02

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Effect of Solvent on Biological Macromolecules

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. Lee, Ph.D.	PSL DCRT
	V. A. Parsegian, Ph.D.	PSL DCRT
	D. Rau, Ph.D.	NIADDK

COOPERATING UNITS (if any)

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Physical Sciences Laboratory

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DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.6	0.5	0.1

Effect of Solvent on Biological Macromolecules

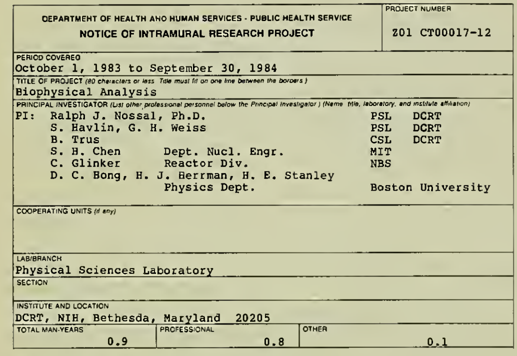
Solvent can generally influence the behavior of macromolecules; an example of this being hydrophobic behavior. Statistical mechanical methods have been used to investigate the origin of thermodynamic properties, such as the Gibbs free energy, enthalpy, and entropy, in relation to hydrophobic interactions.

The theory, so far, is applicable to solutes consisting of spherical molecules only. Work is presently in progress on the development of an approximation scheme that would also be able to deal with solutes composed of nonspherical molecules.

Publications:

Lee, B.: An anatomy of hydrophobicity. *Proc. IMACS Symp. Biomedical Modeling* (in press).

Rau, D. C., Lee, B., and Parsegian, V. A.: Measurement of the repulsive force between polyelectrolyte molecules in ionic solution: hydration force between parallel DNA double helices. *Proc. Natl. Acad. Sci. USA* 81: 2621-2625, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00017-12

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biophysical Analysis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ralph J. Nossal, Ph.D.		PSL	DCRT
	S. Havlin, G. H. Weiss		PSL	DCRT
	B. Trus		CSL	DCRT
	S. H. Chen	Dept. Nucl. Engr.	MIT	
	C. Glinker	Reactor Div.	NBS	
	D. C. Bong, H. J. Berrman, H. E. Stanley	Physics Dept.	Boston University	

COOPERATING UNITS *(if any)*

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DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.9	0.8	0.1

Biophysical Analysis

This project (formerly entitled *Cell Motility and Chemotaxis*) comprises several investigations. Emphasis recently has shifted from investigations of cell locomotion to studies of the structure and dynamics of dense macromolecular systems. Theoretical models using the notion of scaling have been used to study the geometrical and topological characteristics of disordered or irregular media such as gels and branched polymers. Analytical methods and Monte Carlo simulations have been developed to study such parameters as the fractal dimensionality, conductivity, and diffusion exponents of percolation lattices.

Small angle neutron scattering (SANS) studies have been performed to determine structural ordering that occurs between macromolecules in dense solutions of biopolymers. Procedures for deducing intermolecular forces from experimentally determined structure factors are being developed.

Publications:

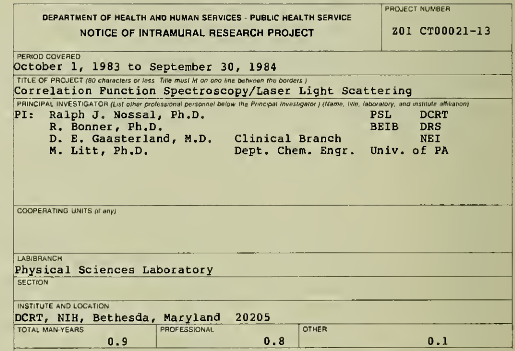
Ben-Avraham, D., and Havlin, S.: Self-Avoiding Walks on Finitely Ramified Fractals. *Phys. Rev.* 29: 2309-2312, 1984.

Havlin, S., Ben-Avraham, D., and Movshovitz, D.: Percolation on Fractal Lattices. *Phys. Rev. Lett.* 51: 2347-2350, 1983.

Havlin, S., and Nossal, R.: Topological Structure of Percolation Clusters. *J. Phys. A. (Math. Gen.)* 17: L427-L430, 1984.

Havlin, S., Trus, B., and Stanley, H. E.: Cluster Growth Model for Branched Polymers that are Chemically Linear. *Phys. Rev. Lett.* (in press).

Hong, D. C., Havlin, S., Hermann, H. J., and Stanley, H. E.: Breakdown of Alexander-Orbach Conjecture for Percolation. Exact Enumeration of Random Walks on the Percolation Backbone. *Phys. Rev.* (in press).



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00021-13

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Correlation Function Spectroscopy/Laser Light Scattering

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ralph J. Nossal, Ph.D.		PSL	DCRT
	R. Bonner, Ph.D.		BEIB	DRS
	D. E. Gaasterland, M.D.	Clinical Branch		NEI
	M. Litt, Ph.D.	Dept. Chem. Engr.	Univ. of PA	

COOPERATING UNITS *(if any)*

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DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.9	0.8	0.1

Correlation Function Spectroscopy/Laser Light Scattering

Various studies utilizing laser light scattering have been undertaken, some in direct support of biomedical research being performed at NIH and similar institutions, others as part of a long-term technical development program. Recent emphasis has been on elucidating physical properties of polymer networks and dense polymer solutions.

New methods have been devised for analyzing dynamic light scattering measurements of the gelation and elasticity of polymer lattices. These procedures facilitate determination of phase plane contours for sol-gel transitions (e.g., relationships between initial monomer concentration and cross-linking density necessary for gelation to occur) and estimation of the number and lengths of the strands that constitute a network. The protocols thus devised can be used to analyze biological gels such as fibrin clots and cytoplasmic networks. Polyacrylamide gels have been used as models in controlled physical studies.

Also, an investigation has been initiated on the manner in which pulsed infrared radiation causes optical breakdown and plasma formation in polymer gels. This study is being performed in support of several investigations of the use of YAG lasers to perform vitreous surgery and other opthalmologic procedures.

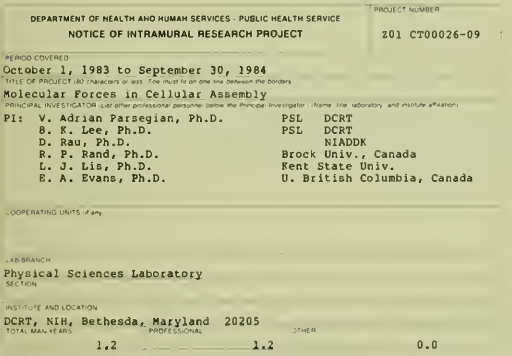
Publications:

Nossal, R.: Network formation in polyacrylamide gels. *Macromolecules* (in press).

Nossal, R., Weiss, G. H., Nandi, P. K., Lippoldt, R. E., and Edelhoch, H.: Sizes and mass distribution of clathrin coated vesicles from bovine brain. *Arch. Biochem. Biophys.* 226: 593-603, 1983.

Steiner, C. A., Litt, M., and Nossal, R: Applications of dynamic light scattering to studies of mucin structure. *Biorheology* 21, 1984.

Steiner, C. A., Litt, M., and Nossal, R: Effects of calcium ions on the structure of canine tracheal mucin. *Biorheology* 21, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00026-09

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Molecular Forces in Cellular Assembly

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	V. Adrian Parsegian, Ph.D.	PSL	DCRT
	B. K. Lee, Ph.D.	PSL	DCRT
	D. Rau, Ph.D.		NIADDK
	R. P. Rand, Ph.D.	Brock Univ., Canada	
	L. J. Lis, Ph.D.	Kent State Univ.	
	E. A. Evans, Ph.D.	U. British Columbia, Canada	

COOPERATING UNITS (if any)

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DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
1.2	1.2	0.0

Molecular Forces in Cellular Assembly

Measurement of forces between DNA molecules has been extended, leading to the discovery of attractive forces due to water "bridges" between properly structured molecular surfaces. The effects of several condensing agents on double helical DNA have been ascertained leading to the conclusion that they act by modifying surface water.

Studies on phospholipid systems have revealed an important link between biochemical changes in lipid composition of the type that can occur on cell membranes and morphological changes of lipid aggregates. They also are beginning to show that electrostatic fields in the vicinity of membranes may be distorted by the same structural features of water that lead to hydration forces.

Publications:

Evans, E. A., and Parsegian, V. A.: Energetics of membrane deformation and adhesion in cell and vesicle aggregation. *Annals N. Y. Acad. Sci.* 416: 13-33, 1983.

Parsegian, V. A.: Dimensions of the 'intermediate' phase of dipalmitoylphosphatidylcholine. *Biophys. J.* 44: 413-415, 1983.

Parsegian, V. A.: Molecular forces governing tight contact between cellular surfaces and substrates. *J. of Prosthetic Dentistry* 49: 838-842, 1983.

Parsegian, V. A., and Rand, R. P.: Membrane interaction and deformation. *Annals N. Y. Acad. Sci.* 416: 1-12, 1983.

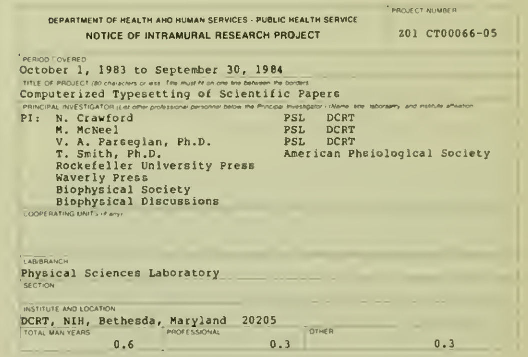
Parsegian, V. A., and Rand, R. P.: Membrane transport and the activity of water near the membrane surface. Physical Methods in the Study of Epithelia. *Membrane Biophysics II.* 283-295, 1983.

Parsegian, V. A., Rand, R. P., and Gingell, D.: Lessons for the study of membrane fusion from membrane interactions in phospholipid systems. *Cell Fusion.* Ciba Found. Symp. 9-27, 1984.

Parsegian, V. A., and Rau, D. C.: Water near intracellular surfaces. *J. Cell Biol.* (in press).

Rand, R. P., and Parsegian, V. A.: Force considerations in model and biological membranes. *Canadian J. Biochem.* (in press).

Rau, D. C., Lee, B., and Parsegian, V. A.: Measurement of the repulsive force between polyelectrolyte molecules in ionic solution: hydration force between parallel DNA double helices. *Proc. Natl. Acad. Sci. USA* 81: 2621-2625, 1984.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00066-05

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Computerized Typesetting of Scientific Papers

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	N. Crawford	PSL	DCRT
	M. McNeel	PSL	DCRT
	V. A. Parsegian, Ph.D.	PSL	DCRT
	T. Smith, Ph.D.	American Phsiological Society	
	Rockefeller University Press		
	Waverly Press		
	Biophysical Society		
	Biophysical Discussions		

COOPERATING UNITS (if any)

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Physical Sciences Laboratory

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INSTITUTE AND LOCATION
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
0.6	0.3	0.3

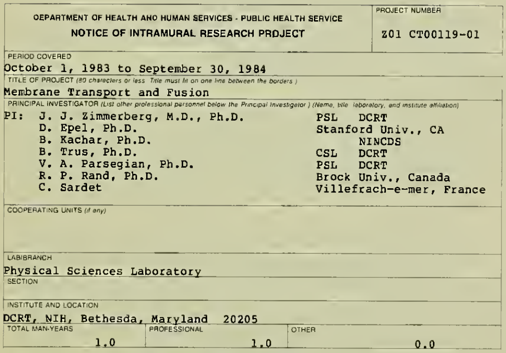
Computerized Typesetting of Scientific Papers

Activities in the past year have allowed us to find many new applications for the techniques being developed to convert word processor and text editor output to typeset pages. We have learned to rely ever more heavily on telephonic transmission.

We have been investigating the interaction of microprocessors with mainframe systems to learn how best to distribute the successive steps of initial keying, correcting, encoding, and typesetting. The IBM-

Personal Computer, PSL Micom, and Osborne units all coordinate with WYLBUR programs and are used to send coded information.

Our activities have attracted attention from different publishing groups in this country and abroad. More and more publishers have shown interest in ways to receive their manuscripts as "compuscripts."



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00119-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Membrane Transport and Fusion

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. J. Zimmerberg, M.D., Ph.D.	PSL DCRT
	D. Epel, Ph.D.	Stanford Univ., CA
	B. Kachar, Ph.D.	NINCDS
	B. Trus, Ph.D.	CSL DCRT
	V. A. Parsegian, Ph.D.	PSL DCRT
	R. P. Rand, Ph.D.	Brock Univ., Canada
	C. Sardet	Villefrach-e-mer, France

COOPERATING UNITS *(if any)*

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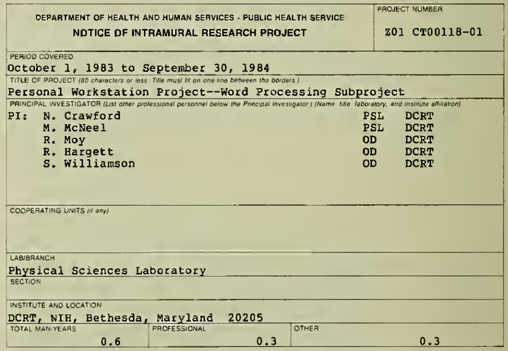
DCRT, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	0.0

Membrane Transport and Fusion

Several experiments have been performed to examine the hypothesis that submembrane granular fusion to cell membranes is driven by granular osmotic pressure, vesicular swelling, and membrane perforation at the point of contact between granular vesicle and cell membrane. A method has been developed to study exocytosis in vitro. Analysis of kinetic parameters reveals a simple dependence of rate of exocytosis on calcium concentration. In clear support of the hypothesis, it has been found that fusion is stopped by the application of inhibitory osmotic pressure of polymeric (dextran) solutions. Image analysis of light micrographs also shows visible granular swelling just prior to disappearance through fusion.

In a separate study of voltage-dependent transmembrane ionic channels, we have been able to measure the volume change occurring with channel opening and closing. Measurements on VDAC, the Voltage Dependent Anion Channel from mitochondria, show very large structural reorganization rather than the traditional gating mechanism usually imagined to control ionic passage. Several other channels are currently under study. It is expected that these volume change measurements, combined with the usual electrochemical and structural approaches, will soon allow critical discrimination between different models of transmembrane ionic channels.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CT00118-01

PERIOD COVERED
October 1, 1983 to September 30, 1984

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Personal Workstation Project--Word Processing Subproject

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. Crawford	PSL	DCRT
	M. McNeel	PSL	DCRT
	R. Moy	OD	DCRT
	R. Hargett	OD	DCRT
	S. Williamson	OD	DCRT

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.6	0.3	0.3

Personal Workstation Project--Word Processing Subproject

PSL representatives have tested and evaluated software packages as part of the DCRT Personal Workstation Project.

Eleven word processing packages have been evaluated to determine the best ones for support by DCRT. Many criteria were used to decide that DisplayWrite2 is the most convenient for NIH needs at this time.

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